



Hypertrophie ventriculaire gauche physiologique ou pathologique : Intérêt d'une approche multiparamétrique

Frédéric Schnell

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Frédéric Schnell. Hypertrophie ventriculaire gauche physiologique ou pathologique : Intérêt d'une approche multiparamétrique. Médecine humaine et pathologie. Université de Rennes, 2015. Français. NNT : 2015REN1B021 . tel-01308520

HAL Id: tel-01308520

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THÈSE / UNIVERSITÉ DE RENNES 1
sous le sceau de l'Université Européenne de Bretagne

pour le grade de
DOCTEUR DE L'UNIVERSITÉ DE RENNES 1

Mention : Biologie et sciences de la santé

Ecole doctorale Vie-Agro-Santé

présentée par

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Préparée à l'unité de recherche UMR 1099
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UFR Médecine

**Hypertrophie
ventriculaire gauche
physiologique ou
pathologique :
Intérêt d'une
approche
multiparamétrique**

**Thèse soutenue à Rennes
le 17 novembre 2015**

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RESUME

Introduction : Le diagnostic de cardiomyopathie hypertrophique (CMH) est difficile chez l'athlète. En effet, le remodelage physiologique induit par l'entraînement physique intense entraîne des modifications électriques et morphologiques qui peuvent mimer une cardiomyopathie. Or il est indispensable de poser le diagnostic de cardiomyopathie avec certitude chez un athlète. Ne pas contre-indiquer un athlète avec une cardiomyopathie l'expose à un risque de mort subite, mais poser un diagnostic par excès l'expose à de lourdes répercussions tant professionnelles que sociales.

Méthodes : (1) Nous avons cherché à améliorer les critères ECG actuels de détection de cardiomyopathie chez l'athlète à partir d'une cohorte multicentrique d'athlètes et de CMH. (2) Nous avons cherché à déterminer quel bilan complémentaire réaliser en cas d'anomalie ECG par un suivi longitudinal d'athlètes avec ondes T négatives. (3) Nous avons essayé de mieux caractériser le phénotype des athlètes atteints de CMH par rapport aux CMH sédentaires dans une cohorte multicentrique. (4) Nous avons tenté de déterminer si l'utilisation des nouvelles techniques d'imagerie de déformation myocardique permettait d'améliorer la pertinence diagnostique et pronostique en cas de CMH dans une cohorte de CMH et d'athlètes rennais.

Résultats : Nous avons proposé une nouvelle classification ECG permettant de mieux identifier les athlètes avec modifications ECG non pathologiques sans diminuer pour autant la capacité à détecter les CMH.

En cas d'ondes T négatives chez l'athlète, nous avons démontré qu'il était indispensable de réaliser une IRM myocardique. En effet l'échocardiographie peut être prise en défaut dans près de 35% des cas.

Néanmoins, les critères diagnostiques actuels de CMH peuvent être pris en défaut; en effet les athlètes avec une CMH ont un phénotype différent des CMH sédentaires avec une meilleure fonction systolique, notamment longitudinale, et diastolique. L'évaluation de la fonction longitudinale à l'effort et l'évaluation de la dispersion mécanique sont des paramètres qui semblent prometteurs en termes de diagnostic. En effet l'altération de la fonction longitudinale semble être en lien avec la fibrose myocardique. L'échocardiographie d'effort, notamment la présence d'une insuffisance mitrale à l'effort, semble être un facteur pronostic important dans les CMH.

Conclusions : les travaux réalisés ont permis de développer des outils pour mieux différencier une hypertrophie ventriculaire gauche (HVG) pathologique d'une HVG physiologique mais également pour mieux caractériser cette HVG et déterminer avec plus de précision le pronostic des CMH.

Mots clés : athlète, hypertrophie ventriculaire, cardiopathie hypertrophique, déformation myocardique.

ABSTRACT

Introduction: the diagnosis of hypertrophic cardiomyopathy (HCM) in athlete is difficult. Indeed, intense sports practice induces an electrical and morphological physiological remodeling which can be difficult to differentiate from the changes induced in pathology.

However, it is essential to diagnose an athlete with a cardiomyopathy. Indeed, in case of underlying cardiomyopathy the athlete will be at risk of sudden cardiac death, but an excessive over diagnosis has strong professional and social consequences.

Methods: (1) we have tried to improve the ECG criteria's, which enable the differentiation between ECG changes induced by exercise and the ECG changes induced by an underlying cardiomyopathy. (2) We tried to define the best investigation algorithm in case of abnormal ECG changes in athletes. (3) We tried to improve the characterization of the phenotype of athletes with HCM as compared to sedentary HCM. (4) We tried to investigate if the use of new imaging technics, i.e. speckle tracking, might improve the diagnostic accuracy and enable a better prognostic evaluation in HCM.

Results: We have proposed a new classification of ECG in athletes enabling to decrease the rate of false positive ECG in athletes without decreasing its diagnostic accuracy in HCM.

In case of pathological T wave inversion (PTWI) in athletes, we demonstrated that a CMR is mandatory, as echocardiography missed a diagnosis of pathology in 35% of PTWI athletes.

Nevertheless, the diagnosis of HCM with current criteria's of HCM can be challenging. Indeed, HCM athletes have a different phenotype from HCM sedentary, with a better systolic and diastolic function; they also have a better longitudinal function.

The assessment of longitudinal function during exercise and mechanical dispersion are promising tool for the diagnosis of HCM in athletes. Indeed, the alteration of longitudinal strain is related to myocardial fibrosis. Exercise echocardiography, i.e. exercise mitral insufficiency, seems to be a prognostic factor in HCM patients.

Conclusions : Ours results enabled to develop tools which might help to better differentiate pathological and physiological left ventricular hypertrophy (LVH); but also to better characterize LVH and the prognosis in HCM patients.

Key words: athlete, left ventricular hypertrophy, hypertrophic cardiomyopathy, speckle tracking

REMERCIEMENTS

Ce projet de thèse n'aurait pas abouti sans la contribution d'un grand nombre de personnes que je tiens à remercier.

Tout d'abord je remercie les rapporteurs de cette thèse, le Docteur Stéphane Nottin et le Professeur Thierry Le Tourneau, qui me font l'honneur de juger mon travail.

Madame le Professeur Geneviève Derumeaux, merci de me faire l'honneur de participer à ce jury, vous qui avez été la première à me suggérer de me lancer dans l'aventure d'une thèse.

Monsieur le Professeur Philippe Mabo, merci de me faire l'honneur de participer à ce jury, et merci pour tous les enseignements et conseils que vous m'avez apportés depuis le début de mon internat à Rennes.

Monsieur le Professeur Erwan Donal, merci d'avoir participé à la direction de cette thèse et surtout un grand merci pour tout ce que tu m'as apporté depuis toutes ces années, notamment dans le domaine de l'échocardiographie.

Monsieur le Professeur François Carré, un grand merci d'avoir accepté de m'encadrer pour cette thèse. Merci pour votre accueil dans le service de médecine du sport et pour ce que vous m'apportez depuis au quotidien.

Merci à tous mes collègues et amis de cardiologie (Vincent, Carine et tous les autres, la liste est trop longue pour citer tout le monde), de médecine du sport (Pierrick, Vincent) et du CIT (Gaëlle et surtout Patricia pour son aide précieuse dans la collection des données). Un grand merci aux personnes que j'ai rencontrées au cours de ces années de thèse et de mobilité: Julián, Nabeel et Guido.

Merci à mes compagnons de thèse Anne, Amélie et David.

Merci à mes amis (Frédéric et Raïssa, Benjamin et Pauline, Charlotte et Fabien et tous les autres qui se reconnaîtront) et à ma famille (mes parents, ma soeur et ma femme Anne- Laure) pour leur soutien au quotidien.

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LISTE DES ABBREVIATIONS

CMH : cardiomyopathie hypertrophique

ECG : électrocardiogramme

ESC : société européenne de cardiologie (european society of cardiology)

FEVG : fraction d'éjection du ventricule gauche

GLS : strain global longitudinal (global longitudinal strain)

HVG : hypertrophie ventriculaire gauche

IRM : imagerie par résonance magnétique

RAo : rétrécissement aortique

VG : ventricule gauche

VNCI : Visite de non contre-indication

Partie 1 : GENERALITES

1. Problématique : remodelage physiologique ou pathologique

L'activité physique intense est responsable d'un remodelage électrique et morphologique physiologique décrit sous le terme de « cœur d'athlète ». Sur le plan morphologique, ce remodelage est responsable d'une dilatation harmonieuse des cavités cardiaques ¹. Cette dilatation cavitaire peut également être associée à une hypertrophie pariétale ventriculaire gauche ². Le caractère harmonieux et modéré du remodelage physiologique permet le plus souvent de le distinguer facilement d'un remodelage pathologique tel qu'observé dans la cardiomyopathie hypertrophique (CMH), la cardiomyopathie dilatée (CMD), la non compaction du ventricule gauche (NCVG) et la cardiomyopathie arythmogène du ventricule droit (CAVD) (Figure1). Mais dans près de 5% des cas, un doute peut exister quant à la présence d'une cardiomyopathie ¹.

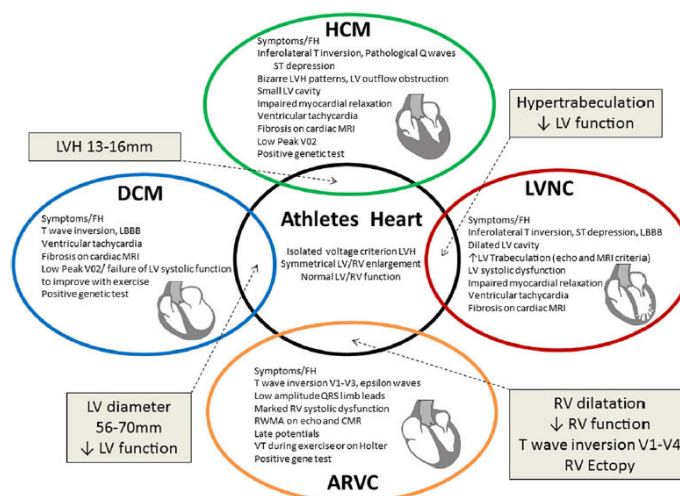


Figure 1 : diagnostic différentiel du cœur d'athlète.

D'après Sharma S et al. Eur H J 2015

La CMH est la principale cause de mort subite de l'athlète ³, c'est pourquoi les recommandations européennes et américaines contre indiquent la pratique du sport intense chez les athlètes atteints de cette pathologie ^{4,5}. Il est donc indispensable de ne pas passer à côté de ce diagnostic, notamment chez un athlète professionnel pour ne pas l'exposer à un

risque de mort subite ; mais il ne faut pas contre-indiquer un athlète sur un simple doute diagnostique car ceci peut avoir de lourdes conséquences sur le plan professionnel et familial.

2. Définition de l'athlète

La définition d'un athlète n'est pas consensuelle, en effet elle varie grandement en fonction des études ⁶. La définition généralement retenue, bien qu'empirique, est la pratique de plus de 6 heures de sport intense par semaine depuis plus de 6 mois ; le sport intense étant défini comme une pratique au-dessus du seuil d'essoufflement ⁷. Ce n'est qu'au dessus de ce niveau d'entraînement que vont se manifester les modifications caractéristiques du cœur d'athlète. Ce remodelage, variable sur le plan interindividuel, est plus marqué chez les athlètes pratiquant des sports d'endurance ⁸.

3. Définition de la cardiopathie hypertrophique

La CMH est définie selon les dernières recommandations européennes par la présence d'une épaisseur pariétale élevée, non expliquée par des conditions anormales de charge ⁹. Sa prévalence est estimée à 0.002 - 0.23 % des adultes. Dans la majorité des cas (60%), il s'agit d'une affection héréditaire à transmission autosomique dominante en lien avec une mutation d'un gène codant pour une protéine sarcomérique. Dans ce manuscrit, nous traiterons uniquement de ces CMH sarcomériques. Il existe d'autres causes plus rares de CMH, telles que les maladies métaboliques héréditaires, les cardiopathies mitochondriales, les maladies neuromusculaires, les syndromes malformatifs et les maladies infiltratives.

Le diagnostic de CMH est basé principalement sur des critères d'imagerie. En effet, le diagnostic est basé sur la détection d'une hypertrophie pariétale $\geq 15\text{mm}$, en l'absence de conditions de charge anormales (HTA, rétrécissement aortique, etc). Le diagnostic peut également être retenu sur une épaisseur pariétale plus faible de 13-14mm, mais dans ce cas, le diagnostic de CMH nécessite des arguments supplémentaires tels qu'une histoire familiale, des anomalies ECG ou des arguments apportés par des tests biologiques ou d'imagerie (fibrose myocardique, anomalie morphologique de l'appareil valvulaire mitral, etc.).

4. Remodelage électrique de l'athlète

La réalisation d'un ECG est recommandée tant par les sociétés européenne¹⁰ que française de cardiologie² comme outil de dépistage de cardiopathie à risque arythmogène chez l'athlète. En effet, dans la majorité des cardiopathies héréditaires l'ECG est modifié^{1,11,12}.

En cas de CMH, l'ECG est pathologique dans 94% des cas, associant des modifications telles que HVG, ondes Q, sous-décalage du segment ST et ondes T négatives⁹. Compte tenu du remodelage électrique présent chez l'athlète, il est parfois difficile de différencier les remodelages physiologique et pathologique.

Plusieurs classifications ECG ont été proposées pour aider à distinguer le remodelage physiologique de l'athlète des modifications induites par les pathologies^{11,13}. Néanmoins elles ne sont pas parfaites et il existe un taux de faux positifs toujours trop élevé. Ceci est à l'origine d'un surcoût pour la société, mais également source d'anxiété chez les athlètes chez qui une anomalie a été diagnostiquée. Les opposants à la réalisation d'un ECG systématique lors de la visite de non contre indication (VNCI) à la pratique sportive en compétition évoquent le risque élevé de faux positifs comme frein à la généralisation de ces recommandations¹⁴.

Les recommandations européennes de 2010 ont classé les anomalies ECG comme normales et étant liées au sport, ne nécessitant donc pas la réalisation d'examens complémentaires ; ou comme anormales et non liées au sport, nécessitant donc la réalisation d'examens complémentaires.

Classique chez l'athlète	Non lié au sport
Bradycardie sinusale BAV du premier degré BBD incomplet Repolarisation précoce Critères isolés d'HVG électrique	Ondes T négatives Sous-décalage du segment ST Ondes Q pathologiques Pré-excitation ventriculaire BBD complet ou BBG complet Intervalle QT long ou court Syndrome de Brugada Arythmies supra-ventriculaires complexes Arythmies ventriculaires Hypertrophie atriale gauche Déviation axiale gauche / HBAG Déviation axiale droite / HBPG Hypertrophie VD
Classification des anomalies ECG chez l'athlète. D'après Corrado et al Eur Heart J 2010	

Ces recommandations ont été actualisées en 2013 lors des critères de Seattle. Les nouveautés étaient principalement de considérer les ondes T négatives biphasiques de l'Afro-caribéen comme une manifestation de repolarisation précoce favorisée par le sport, non pathologique.

Normal chez l'athlète	ECG anormal chez l'athlète
<p>Bradycardie sinusale (≥ 30 bpm)</p> <p>Arythmie sinusale</p> <p>Rythme jonctionnel</p> <p>BAV du premier degré (PR > 200 ms)</p> <p>BAV 2 Mobitz 1 (Wenckebach)</p> <p>BBD incomplet</p> <p>Critères isolés d'HVG électrique</p> <p style="padding-left: 20px;">Hormis HVG électrique associée à hypertrophie atriale gauche, déviation axiale gauche, sous décalage ST, ondes T négatives ou ondes Q pathologiques</p> <p>Repolarisation précoce</p> <p>Surélévation convexe « en dôme » du segment ST associé avec des ondes T négatives de V1 à V4 chez l'athlète Afro caribéen</p>	<p>Ondes T négatives :</p> <p>> 1 mm dans 2 ou plus dérivations de V2 à V6, II et AVF, ou I et AVL (sauf III, AVR et V1)</p> <p>Sous-décalage du segment ST :</p> <p>≥ 0.5 mm dans ≥ 2 dérivations</p> <p>Ondes Q pathologiques:</p> <p>> 3 mm ou > 40 ms dans ≥ 2 dérivations (sauf III et aVR)</p> <p>BBG complet</p> <p>QRS ≥ 120 ms, QRS à prédominance négative en V1 + onde R monophasique en I et V6</p> <p>Délai de conduction intra ventriculaire :</p> <p>QRS > 140 ms</p> <p>Déviation axiale gauche :</p> <p>-30° à -90°</p> <p>Hypertrophie atriale gauche :</p> <p>P > 120 ms en I ou II avec portion négative ≥ 1 mm et ≥ 40 ms en V1</p> <p>Hypertrophie VD :</p> <p>RV1+SV5 > 10 mm + déviation axiale droite $> 120^\circ$</p> <p>Pré-excitation ventriculaire :</p> <p>PR < 120 ms + onde delta et QRS > 120 ms</p> <p>Intervalle QT long :</p> <p>QTc ≥ 470 ms (homme) ; 480 ms (femme) ; 500 ms (prolongation QT marquée)</p> <p>Intervalle QT court :</p> <p>QTc ≤ 340 ms</p> <p>Syndrome de Brugada</p> <p>Bradycardie sinusale marquée < 30 bpm ou pauses sinusales ≥ 3 s</p> <p>Tachycardies atriales :</p> <p>tachycardie supraventriculaire, fibrillation atriale, flutter atrial</p> <p>ESV :</p> <p>≥ 2 ESV sur un tracé de 10 sec</p> <p>Arythmie ventriculaire :</p> <p>doublets, triplets et TVNS</p>
<p>Classification des anomalies ECG chez l'athlète.</p> <p>D'après Drezner et al BJSM 2013</p>	

Néanmoins, malgré l'amélioration incontestable apportée par cette classification, il persiste de nombreux faux positifs nécessitant donc d'affiner encore cette classification.

5. Remodelage morphologique de l'athlète

Le remodelage électrique de l'athlète peut s'accompagner d'un remodelage morphologique. Il se traduit en premier lieu par une dilatation harmonieuse des 4 cavités. Cette dilatation des cavités permet au cœur d'athlète d'éjecter un volume d'éjection normal tout en ayant une fréquence cardiaque et parfois même une fraction d'éjection moindres. Ceci permet à l'athlète d'avoir un débit cardiaque à l'effort plus élevé que le sédentaire. Il a d'ailleurs été démontré que les capacités fonctionnelles de l'athlète (pic de VO₂) étaient plus reliées à la masse du ventricule gauche (VG) qu'à la fonction VG¹⁵. Cette dilatation cardiaque s'accompagne d'une hypertrophie pariétale du VG adaptée et harmonieuse⁶.

Concernant les parois, leur remodelage physiologique chez l'athlète peut parfois mimer une cardiopathie hypertrophique. En effet, 1.5% des athlètes peuvent avoir une hypertrophie pariétale supérieure à 12 mm¹⁶ (Figure 2). Ceci est particulièrement vrai chez les athlètes masculins afro-caribéen chez qui des épaisseurs pariétales de plus de 16 mm peuvent être constatées sans pour autant que le diagnostic de CMH ne soit retenu¹⁷.

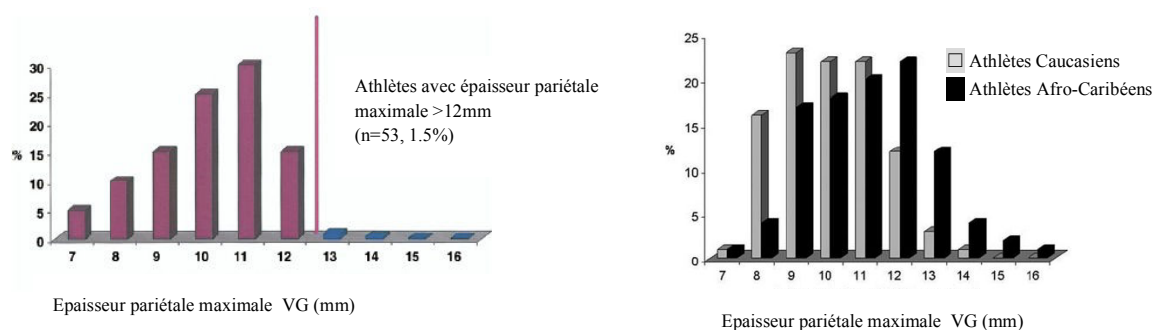


Figure 2 : influence de l'éthnie sur le remodelage hypertrophique

D'après Basavarajaiah et al. JACC 2008 et Rawlins et al, Eur J Echo 2009

Dans les années 70, Morganroth a développé une théorie selon laquelle le remodelage serait différent en fonction du type d'activité physique¹⁸. Sur une étude observationnelle transversale de 56 athlètes, est née la croyance que le remodelage des athlètes endurants serait excentrique et le remodelage des athlètes de « résistance » serait concentrique. Cette hypothèse est depuis fortement remise en cause^{19,21}, notamment par une étude longitudinale

de Spence et al. ²² Ce travail, basé sur l'étude de 23 sédentaires soumis de manière randomisée à 6 mois d'entraînement en endurance ou en résistance, a confirmé le remodelage excentrique en cas d'entraînement en endurance, mais n'a pas réussi à démontrer un remodelage concentrique chez l'athlète entraîné en résistance. Il est donc à retenir qu'il ne peut pas y avoir de remodelage hypertrophique physiologique sans dilatation VG associée chez un athlète.

6. Critères diagnostiques d'HVG physiologique et pathologique : une approche multiparamétrique

6.1. Différences physiopathologiques

L'hypertrophie du sportif est secondaire à différents déterminants, hémodynamiques, neuro-humoraux et génétiques, agissant en synergie. L'exercice va entraîner un remodelage physiologique adaptatif au niveau du myocarde avec une hypertrophie adaptée des cardiomyocytes ^{23,24}. Ce remodelage met en jeu de voies de signalisation différentes de celles qui interviennent dans le remodelage pathologique (Figure 3) ²⁵. Les données expérimentales animales ont précisé que cette hypertrophie était modérée et équilibrée, sans fibrose ²⁶ et avec une densité capillaire adaptée par rapport à l'hypertrophie myocytaire ²⁷. Par conséquent le remodelage de l'athlète est constitué de tissu sain.

A l'inverse, dans le cas de l'HVG pathologique il existe une diminution du nombre de myocytes, une hypertrophie et une déstructuration des myocytes restants, avec réexpression du programme génique foetal et une fibrose interstitielle. La désorganisation des cardiomyocytes est associée à des anomalies des petites artères coronaires intra murales avec réduction de la réserve coronaire, responsable avec l'augmentation de la masse musculaire, de plages de nécrose et fibrose ischémiques. Cette hypertrophie est par conséquent responsable d'une diminution de la compliance du VG ²⁵.

Voies de signalisation du remodelage hypertrophique

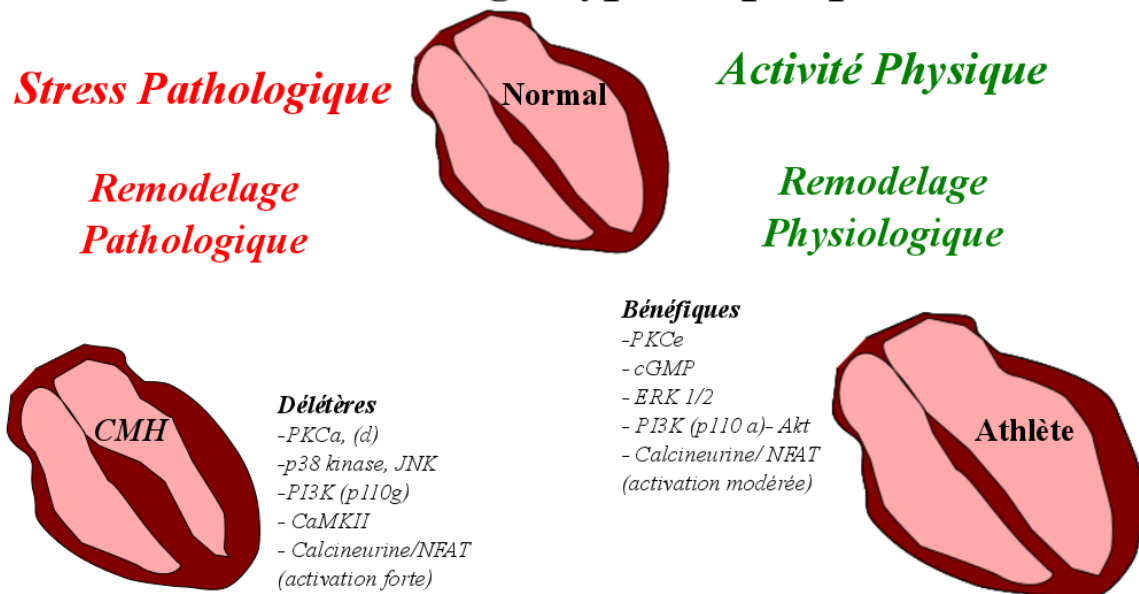


Figure 3 : les différentes voies de signalisation du remodelage hypertrophique

6.2. Différences cliniques

Les dernières recommandations de la société européenne de cardiologie (ESC) ont clairement abordées les critères diagnostiques de CMH chez l'athlète (figure 5). Comme les critères développés par Maron et al. dans Circulation en 2006 ³, ces recommandations insistent sur l'approche multiparamétrique nécessaire au diagnostic de CMH dans cette population. En effet, les données démographiques, ECG, morphologiques et fonctionnelles doivent être prises en compte. On remarquera que tous les niveaux de preuves sont faibles (niveau de preuve B ou C uniquement).

Ce faible niveau de preuve souligne l'importance de réaliser des études multicentriques comportant un nombre plus important d'athlètes afin que les recommandations ne soient pas basées uniquement sur des « avis d'experts »

Web Table 7: Clinical features that favour the diagnosis of hypertrophic cardiomyopathy in elite athletes with maximal left ventricular wall thickness 12–15 mm

Category	Feature	Level of evidence	References
A. Demographics			
	Family history of hypertrophic cardiomyopathy in first degree relative(s)	B	9, 460
	Female gender	B	446, 447
	Family history of sudden cardiac death in first degree relative(s) ≤40 years	C	
	Cardiovascular symptoms (unexplained syncope, disproportionate dyspnoea on exertion, chest pain, palpitations)	C	
B. ECG			
	Abnormal Q waves in at least two leads from II, III, aVF (absence of left anterior hemiblock), V1–V4, I, aVL, V5–V6	B	450–452
	Inverted T-waves in two or more leads from lead groups II, III, aVF or/and I, aVL, V5–V6	B	450–452
	Inverted T-waves V2–V4 (>16 years old) ^a	B	450–452
	Giant negative T-waves in two contiguous leads (> 5mm)	B	450–452
	Inverted T-waves in leads V2–V4 (<16 years old)	B	450–452
	Complex ventricular arrhythmias at 24 h Holter rhythm recording or >2000 PVCs/24 h	B	448, 449
C. Structural			
	Asymmetrical interventricular septal hypertrophy (septal to posterior wall thickness ≥1.5)	B	445, 446, 455, 456
	Complete SAM of mitral valve	B	445, 446, 455, 456
	Left ventricular end diastolic diameter <45 mm	B	445, 446, 455, 456
	Late gadolinium enhancement on CMR	C	
	Resting intraventricular gradient	C	
	Incomplete SAM of mitral valve	B	445, 446, 455, 456
	Left ventricular hypertrophy of the anterior septum or the posterior wall ≥12 mm	B	445, 446, 455, 456
	Left atrium >45 mm	C	
	Right ventricular hypertrophy (right ventricular subcostal thickness >5 mm)	C	
	Myocardial crypts identified with CMR	C	
D. Functional			
	Mitral inflow pattern E<A (<20 years old)	B	453, 454
	Tissue Doppler Imaging: Ea <9 cm/sec	C	
	Tissue Doppler Imaging: Sa <9 cm/sec	C	
	Increased BNP	C	
	Ea 10–13 cm/sec	C	
	Diastolic radial strain <7 cm/sec	C	
	VO ₂ max <50ml/kg/min or <120% of predicted VO ₂ max (uncommon in endurance athletes)	C	
	Increased left ventricular torsion	C	
E. Detraining			
	No response to detraining for 3 months	B	453, 454
F. Genetics			
	Disease causing sarcomere mutation	B	455, 456

BNP = brain natriuretic peptide; CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; PVCs = premature ventricular contractions; SAM = systolic anterior motion.

^aException to T wave inversion: elevated ST-segment with an upward ('domed') convexity, followed by a negative T wave in V1–V4, is a common pattern of early repolarisation seen in adult and adolescent athletes of African-Caribbean descent and it should be considered a minor criterion for this ethnic group. However, T wave inversion in the lateral or inferolateral leads (V5–V6, I and aVL, II and aVF), regardless of ethnicity, is considered a major criterion and requires additional testing to rule out hypertrophic cardiomyopathy.^{452,457,458}

Figure 4 : Critères diagnostiques pour différencier cœur d'athlète et CMH

D'après les Recommandation ESC 2014 sur le diagnostic et la prise en charge des CMH, Eur Heart J, 2014 ; web addenda

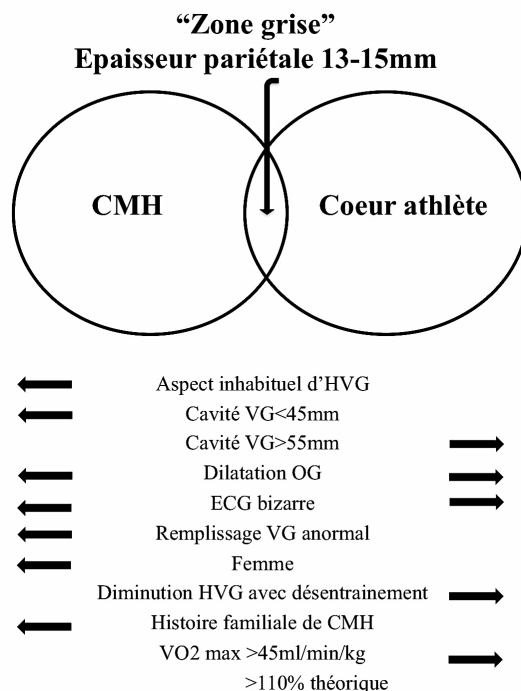


Figure 5 : Critères diagnostiques de CMH chez l'athlète

D'après Maron et al. Circulation 2006

6.2.1. Clinique, histoire familiale et génétique

Une histoire familiale de mort subite est un élément majeur dans le dépistage de l'athlète et justifie à lui seul un avis cardiologique et la réalisation d'examens complémentaires appropriés ¹⁰. En cas de doute sur le diagnostique, cet élément sera fondamental à prendre en compte, c'est pour cela qu'il est systématiquement recherché via un questionnaire spécifique de la société française de médecine de l'exercice et du sport. Néanmoins, l'athlète peut volontairement omettre ce type d'information de nature à arrêter sa carrière ; et chez les athlètes internationaux il n'est pas évident de récupérer les antécédents familiaux précis.

6.2.2. Apport de l'ECG

Comme décrit précédemment la réalisation d'un ECG est préconisée en France lors de la VNCI à la pratique d'un sport en compétition. Il est admis que l'HVG électrique isolée n'est

pas un critère orientant vers une CMH, mais qu'il faut se méfier des ondes Q pathologiques, des ondes T négatives notamment en latéral ainsi que des sous-décalages du segment ST^{11,13}. Compte tenu de l'importance persistante d'un nombre des faux positifs important, il reste nécessaire de mieux définir les critères de normalité ECG chez l'athlète.

Par ailleurs, dans les recommandations il n'est pas défini jusqu'où aller dans la poursuite des examens complémentaires en cas d'ondes T négatives. Une précédente étude de Pelliccia avait démontré que les ondes T négatives n'étaient pas normales chez l'athlète, mais que fréquemment le diagnostic n'avait été fait que grâce au suivi²⁸. Il semble indispensable de préciser si une échocardiographie et un test d'effort suffisent à écarter tout doute quant à une cardiopathie sous-jacente ou si de plus amples examens doivent être réalisés.

6.2.3. Apport de l'échocardiographie

Hormis l'épaisseur pariétale (≥ 15 mm ou ≥ 13 mm en cas de forme familiale), de nombreux critères doivent être pris en compte de manière additionnelle lors de la réalisation du diagnostic de CMH chez l'athlète. En effet, une petite cavité VG associée à une hypertrophie importante est plus évocatrice d'une CMH. Ceci est également vrai devant l'observation d'une hypertrophie asymétrique, d'une altération de la fonction diastolique, d'une dilatation atriale, d'anomalies associées de l'appareil mitral ou en présence de fibrose myocardique^{3,9}.

Les nouvelles techniques de déformations myocardiques (speckle tracking) permettent une meilleure évaluation de la fonction systolique. L'évaluation de la fonction longitudinale VG dans le cadre des CMH est recommandée dans un récent consensus d'experts³⁵. Par ailleurs, une corrélation entre fibrose en IRM et altération des déformations myocardiques a déjà été démontrée dans des études portant sur des petites cohortes, nécessitant encore des études de validation^{36,37}. Malgré ces nombreuses publications montrant l'intérêt du 2D strain longitudinal dans l'évaluation des cardiomyopathies hypertrophiques²⁹⁻³³, les données de strain longitudinal n'ont pas été retenues comme pertinentes pour différencier cœur d'athlète et CMH dans les dernières recommandations de l'ESC. Ceci concorde avec un récent consensus d'experts de l'European Association of Cardiovascular Imaging (EACVI)³⁴ qui concluait lui aussi que les données sur le 2D strain étaient trop préliminaires pour permettre de différencier les 2 types de remodelage.

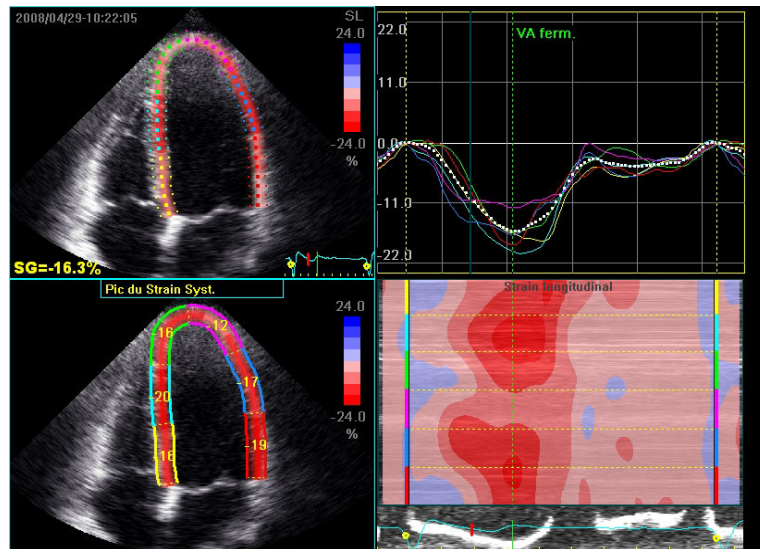


Figure 6 : Exemple de courbe de strain longitudinal, déterminé à partir d'une coupe apicale 4 cavités (données personnelles)

L'échocardiographie à l'effort : cette nouvelle modalité d'imagerie permet de rechercher un gradient intra-ventriculaire à l'effort. Il est donc recommandé de réaliser cet examen en cas de dyspnée chez un patient porteur de CMH et chez les patients asymptomatiques lorsque cela influe sur des modifications des conditions de vie ou le traitement ⁹. Ceci semble donc un outil intéressant dans la prise en charge des sujets et dans la stratification du risque pour la pratique du sport intense. Peu d'études ont pour le moment évalué son intérêt pour différencier cœur d'athlète et CMH. L'intérêt et la faisabilité de l'étude des déformations myocardiques à l'effort ont déjà été démontrés dans les CMH ³² et chez les athlètes ³⁸ ; mais aucune étude n'a démontré son intérêt dans la différenciation de l'HVG physiologique et pathologique.

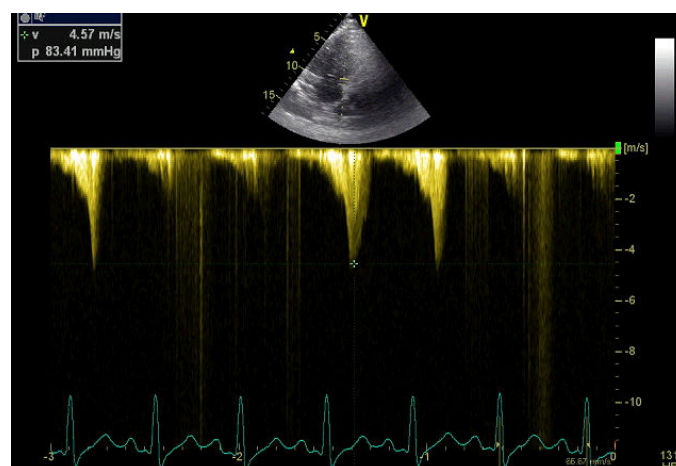


Figure 7 : Exemple de gradient intra ventriculaire gauche à l'effort (données personnelles)

6.2.4. Apport de l'IRM cardiaque:

L'IRM est le gold standard dans l'évaluation de l'épaisseur pariétale, mais surtout cet examen permet également de réaliser une caractérisation tissulaire par l'étude du rehaussement tardif. Le rehaussement tardif est un élément très intéressant dans la différenciation des hypertrophies physiologique et pathologique. En effet, en cas d'épaisseur pariétale limite, la présence de rehaussement tardif permet d'affirmer que le remodelage est pathologique puisque le rehaussement tardif est en lien avec une fibrose myocardique ³⁹. Il est à rappeler que l'absence de rehaussement tardif n'élimine absolument pas le diagnostic de CMH ⁹ puisque la plupart des études rapportent la présence de rehaussement tardif chez au moins 50% des patients atteints de CMH ^{37-36,40}.

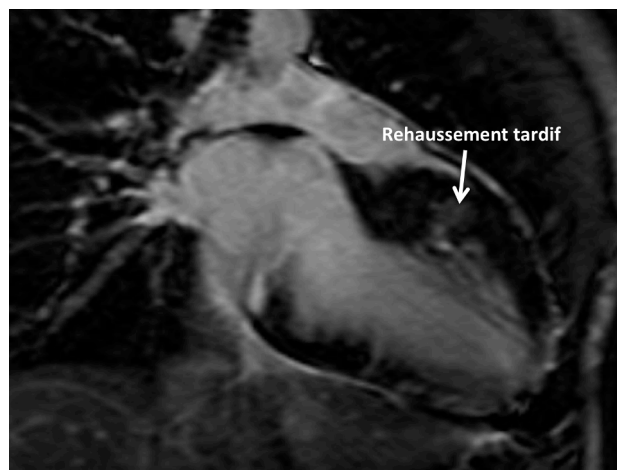


Figure 8 : Exemple de séquence IRM de rehaussement tardif chez un patient atteint de CMH (données personnelles)

6.2.5. Apport de l'épreuve d'effort cardio-pulmonaire

Les recommandations concernant la VO₂ reposent sur une étude de Sharma et al. ⁴¹. Cette étude a démontré qu'en cas d'HVG modérée chez un athlète sans anomalie ECG et sans antécédents familiaux de CMH, un pic de VO₂ >50 ml/min/kg ou >20% au dessus de la valeur prédite permettait de rassurer l'athlète sur le caractère physiologique de son hypertrophie. Néanmoins, ce critère n'est pas absolu et il est possible de rencontrer des athlètes de haut niveau porteurs d'une véritable CMH capables de battre des records ^{42,43}.

6.2.6. Apport du désentraînement

La régression de l'hypertrophie est un critère majeur en faveur d'un remodelage

physiologique ⁴⁴⁻⁴⁶. Néanmoins, le désentraînement est généralement mal accepté par les athlètes, ceci explique pourquoi ce critère n'est utilisé qu'en dernière intention chez l'athlète.

6.2.7. Apport des tests génétiques

La CMH étant une maladie génétique, la réalisation de tests génétiques à la recherche de mutations est actuellement recommandée par les sociétés savantes. Les mutations les plus fréquentes sont celles touchant les gènes codant pour la chaîne lourde beta de la myosine (MYH7) et la protéine C cardiaque (MYBPC3), les mutations touchant les gènes codant pour les troponines I et T (TNNI3, TNNT2), la chaîne alpha 1 de la tropomyosine (TPM1) et la chaîne légère de la myosine 3 (MYL3) sont moins fréquentes.

Des études ont montré que le pronostic pouvait dépendre du type de mutation ⁴⁷. Environ 5% des sujets atteints de CMH peuvent présenter des mutations multiples de protéines sarcomériques, il semble que ces sujets présentent un phénotype plus précoce et plus sévère que les autres patients ⁴⁸. Néanmoins, l'application en routine des tests génétiques afin de distinguer CMH et cœur d'athlète reste difficile compte tenu de la présence de nombreux variants de signification pathologique inconnue qui en rend l'interprétation délicate.

Partie 2 : HYPOTHESES ET OBJECTIFS DE NOS TRAVAUX

Dans ce travail, nous avons tenté d'améliorer les outils à notre disposition afin de mieux différencier l'HVG physiologique de l'athlète de l'HVG pathologique.

1. Améliorer le dépistage des athlètes

Tout d'abord, nous avons essayé d'améliorer le dépistage des CMH dans la population des athlètes en améliorant la classification des ECG chez l'athlète. En effet, l'ECG est l'examen de dépistage de 1^{ère} intention chez l'athlète, puisque sa réalisation est recommandée tant par les sociétés européenne¹⁰ que française de cardiologie². Les détracteurs de l'ECG comme outils de dépistage lui reprochent son fort taux de faux positifs¹⁴.

Ainsi, dans un 1^{er} temps, lors d'un travail collaboratif nous avons cherché à améliorer la classification d'interprétation de l'ECG de l'athlète, en visant à diminuer le taux de faux positifs sans altérer la spécificité pour dépister les CMH.

Ce travail collaboratif, dans lequel nous avons participé activement nous a permis de définir une population particulièrement à risque de présenter une pathologie, à savoir les athlètes avec ondes T négatives pathologiques. En effet, ce type d'anomalie ECG est retrouvé très fréquemment en cas de CMH⁹. Nous avons ensuite défini le bilan complémentaire à réaliser chez l'athlète en cas d'observation d'ondes T négatives sur l'ECG de repos.

2. CMH chez l'athlète, un phénotype morphologique particulier

Dans les articles précédents, nous nous sommes basé sur les données d'imagerie pour faire le diagnostic de CMH, ceci à partir des critères validés par la société européenne de cardiologie⁹. Néanmoins malgré ces critères, il n'est pas toujours facile de faire la différence entre le remodelage morphologique physiologique de l'athlète et le remodelage pathologique de la CMH. En effet, les critères actuels sont malheureusement basés sur des études comparant des CMH sédentaires avec des sportifs non pathologiques. Il nous paraissait que ces études comportaient donc un biais majeur. Nous avons comparé dans une étude collaborative des

athlètes présentant des CMH confirmée avec des sédentaires porteurs de CMH, afin de déterminer si les athlètes avec CMH avaient un phénotype différent. Compte tenu de la faible incidence des athlètes avec CMH, nous avons collaboré avec l'équipe du St Georges Hospital de Londres en mettant en commun nos données respectives pour mener à bien ce projet.

3. Apport des nouvelles techniques de déformations myocardiques

Malgré l'apport non négligeable des données échocardiographiques et IRM utilisées en routine clinique, il nous est apparu que les critères diagnostiques de CMH faisaient encore débat. Nous avons donc souhaité utiliser des paramètres plus sensibles tels que l'étude des déformations myocardiques au repos.

Partant du principe que le remodelage du cœur d'athlète est adapté pour l'effort, nous avons également émis l'hypothèse qu'il pourrait être pertinent d'évaluer les déformations myocardiques à l'effort. La seule information validée pour le moment, est la recherche d'un gradient à l'effort dans les CMH symptomatiques. Mais peu d'études se sont intéressées à l'apport des paramètres de déformations myocardique à l'effort dans les CMH.

Compte tenu de la faible prévalence des CMH chez les sportifs, nous avons souhaité tout d'abord valider ce concept dans notre population globale de CMH, mais également dans d'autres types d'hypertrophie pathologique comme les rétrécissement aortiques. Dans la dernière partie nous avons utilisés ces concepts pour essayer de mieux caractériser les athlètes porteurs de CMH.

Nous avons donc étudié :

- 3.1. La pertinence de l'étude des déformations myocardiques au repos comme outil de caractérisation tissulaire, en comparant les données de déformations myocardique et de fibrose myocardique (via le rehaussement tardif en IRM).
- 3.2. Puis nous avons étudié la valeur ajoutée de l'échocardiographie d'effort comme élément de diagnostic et de pronostic en intégrant les données de déformations myocardiques à l'effort.
- 3.3. Finalement nous avons appliqué ces techniques dans la population des athlètes porteurs de CMH pour vérifier leur apport dans la différenciation du remodelage physiologique et pathologique.

Partie 3 : METHODES

1. Population

Les populations d'athlètes avec anomalies cardiaques, que ce soit ondes T négatives pathologiques ou CMH étiquetées, ne sont pas fréquentes. Ceci explique que la majorité des études de ce mémoire ont été menées en collaboration avec d'autres équipes nationales (CHU de Bordeaux, le réseau du Club des Cardiologues du Sport) ou internationales (St Georges Hospital, London ; ASPETAR, Doha, Qatar).

L'étude des déformations myocardiques n'est pas réalisée dans l'ensemble des centres de cardiologie du sport et les projets collaboratifs nécessitent des centres expérimentés dans cette technique et l'utilisation d'un matériel identique. En effet, les données de 2D strain sont dépendantes de la marque de l'appareil d'échocardiographie et du logiciel d'analyse utilisé. Les travaux de la dernière partie de la thèse utilisant ce type de techniques n'ont donc été réalisés que localement ou en collaboration avec le CHU de Bordeaux.

Les populations incluses comportent :

1. 2 populations contrôles : des sujets sédentaires sains et des athlètes sains
2. des athlètes avec ondes T négatives pathologiques
3. des CMH sportifs et sédentaires ; les critères diagnostiques de CMH retenus étant ceux recommandés par la société européenne de cardiologie ⁹.
4. des patients avec rétrécissement aortique : ces sujets ont été inclus afin de comparer différents types de remodelages hypertrophiques pathologique.

Les critères d'inclusion et d'exclusion spécifiques seront développés dans chacun des différents articles inclus dans ce travail.

2. Acquisition et analyse

Concernant les études multicentriques, les appareils ECG, d'échocardiographie, d'épreuve d'effort avec analyse des échanges gazeux et d'IRM utilisés pour les acquisitions n'ont pas toujours pu être standardisés.

- (i) Les **échocardiographies** ont été réalisées selon les recommandations américaines et européennes de cardiologie ^{49,50}. Concernant la dernière partie du mémoire, portant sur l'intérêt des déformations myocardiques, les acquisitions ont été réalisées sur un type unique d'appareil (Vivid 9, GE, Healthcare, Horten, Norway).

Les échocardiographies ont ensuite été analysées sur une station Echo PAC BT 12 (GE, Healthcare, Horten, Norway). Cette analyse sera développée dans le chapitre suivant.

- (ii) Les **IRM** ont été réalisées selon les recommandations américaines actuelles ⁵¹. La fonction et la morphologie ventriculaire ont été analysées au moyen de séquences de ciné IRM. Des séquences de rehaussement tardif ont été réalisées après injection de gadolinium afin de permettre une caractérisation tissulaire (étude de la fibrose myocardique).
- (iii) Les **épreuves d'effort avec VO₂** ont été réalisées sur l'ergomètre le plus adapté en fonction du type de sport pratiqué, et sur un ergocycle pour les sédentaires. Ces examens ont été réalisés en accord avec les critères de Wasserman ⁵².

3. Analyse de données de déformations myocardiques

Le 2D strain est une mesure de la déformation du myocarde dans une direction. Durant l'activation électromécanique, le myocarde se déforme durant la systole du fait du raccourcissement des sarcomères. En diastole, le ventricule retrouve sa géométrie initiale grâce à la relaxation passive et au remplissage actif suivant la contraction atriale. Comme le tissu myocardique est virtuellement incompressible, le volume occupé par les parois du ventricule demeure fixe durant l'ensemble du cycle cardiaque et se déforme dans les 3 dimensions de l'espace. Cette déformation peut s'exprimer en 3 coordonnées ventriculaires: un raccourcissement longitudinal et circonférentiel, et un épaississement radial, comme représenté dans la figure 9 ⁵³⁻⁵⁵.

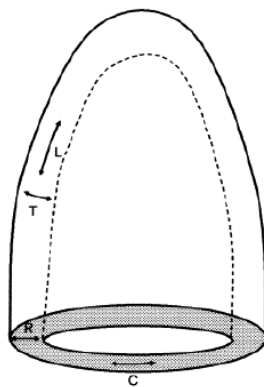


Figure 9 : illustration des différentes composantes de la déformation du myocarde en systole : C= circonférentielle, L=longitudinale, T= transverse, R=radiale.

La déformation du myocarde peut alors s'exprimer grâce à un paramètre en une dimension : le strain (ϵ). Cet indice définit la déformation totale durant le cycle cardiaque, relativement à une longueur initiale mesurée au début du cycle, et s'exprime en pourcentage. Le raccourcissement longitudinal et circonférentiel en systole se traduit par un strain négatif, alors que l'épaississement radial systolique résulte en un strain positif. La valeur locale du strain télé systolique reflète la contractilité régionale et le strain global télé systolique reflète la contractilité globale du VG. En diastole, la valeur du strain tend vers zéro (retour à la longueur initiale du segment au début du cycle cardiaque). Le strain en deux dimensions (2D strain) est une technique utilisant les images acquises en mode bidimensionnel standard pour analyser le speckle tracking (littéralement «suivi de pixels»). Cette technique consiste à identifier les petites hétérogénéités du muscle cardiaque (créées par les interférences acoustiques générées par la réflexion du faisceau ultrasonore sur le myocarde) et à en suivre le déplacement tout au long du cycle cardiaque. Un algorithme informatique suit les changements de géométrie de cet ensemble de pixels, et en calcule le déplacement, la vitesse, le strain et le strain rate. Le speckle tracking est angle indépendant, et la trajectoire des pixels peut être suivie dans toutes les directions. En vue apicale, les paramètres non seulement longitudinaux mais aussi transverses peuvent être calculés, en petit axe on peut également calculer les paramètres radiaux et circonférentiels, pour tous les segments myocardiques. En plus des paramètres de déformation circonférentielle du myocarde, la rotation et la torsion du myocarde peuvent également être analysées. La résolution spatiale et temporelle s'avère bonne. La validation des premiers essais de 2D strain a été effectuée in vitro sur des blocs de gélatine et in vivo chez l'animal ⁵⁶.

PARTIE 4 : RESULTATS

1. Améliorer le dépistage des athlètes

1.1. Classification ECG de l'athlète

Comme décrit dans l'introduction de ce mémoire, l'interprétation de l'ECG de l'athlète est parfois difficile, en effet les modifications induites par le sport intense peuvent mimer une cardiopathie. Une bonne interprétation de l'ECG est donc fondamentale car il s'agit de la première étape du dépistage de l'athlète. La difficulté de cette analyse est double, certaines particularités considérées comme anormales sont liées à la pratique sportive et ne réclament pas de bilan cardiologique complémentaire et d'autre part certaines anomalies ne sont pas liées à la pratique sportive mais ne présentent pas de risque si cette pratique est poursuivie. Pour aider à cette analyse de l'ECG qui est souvent réalisée par des praticiens non familiarisés avec les ECG d'athlètes, nous avons dans ce travail collaboratif cherché à proposer une nouvelle classification d'interprétation de l'ECG de l'athlète, visant à faire baisser le nombre de faux positifs par rapport aux classifications existantes, notamment chez les athlète afro-caribéens^{11,13}.

Apport du candidat dans ce travail

Compte tenu de la difficulté d'inclure des athlètes contrôles pathologiques atteint de CMH, nous avons été sollicités par l'équipe du Professeur Sharma afin de participer à l'inclusion d'athlètes porteurs de CMH. Une grande part de ces patients ont été inclus à Rennes, ils faisaient partie de la base de données prospective de CMH réalisée dans le cadre de cette thèse. J'ai donc participé à l'inclusion de ces sujets et j'ai relu l'ensemble des données ECG, échocardiographiques et IRM. Nous avons participé à la relecture et à la correction du manuscrit.

RESUME DU TRAVAIL

Objectifs: de récents travaux ont visé à améliorer la classification d'interprétation de l'ECG de l'athlète de l'ESC. En effet, ces critères étaient fondés principalement sur l'analyse d'athlètes caucasiens (AC) et ne prenaient en compte ni l'effet de l'ethnie afro-caribéenne ni de nouvelles études portant sur certaines modifications ECG isolées. Nous avons évalué les critères ESC, les critères de Seattle, et des critères ECG affinés sur une cohorte d'AC et d'athlètes afro-caribéens (AAC).

Méthodes et Résultats: entre 2000 and 2012, 1.208 AAC ont été évalués par un interrogatoire, un examen clinique, un ECG et des explorations complémentaires si appropriées. Les ECG ont été analysés de manière rétrospective en accord avec les recommandations ESC, les critères de Seattle et des critères ECG affinés qui excluent certaines spécificités ECG si elles sont présentes isolément. Ces 3 critères ont également été appliqués à 4.297 AC et à 103 athlètes avec cardiomyopathies hypertrophiques (CMH).

Les recommandations ESC faisaient suspecter une anomalie cardiaque chez 40.4% des AAC et 16.2% des AC. Les critères de Seattle ont permis de réduire la suspicion à 18.4% des AAC et 7.1% des AC. Les critères affinés ont permis une réduction supplémentaire à 11.5% des AAC et 5.3% des AC. Les 3 critères ont permis d'identifier 98.1% des athlètes avec CMH. En comparaison avec les critères ESC, les critères affinés ont permis d'améliorer la spécificité de 40.3% à 84.2% chez les AAC et de 73.8% à 94.1% chez les AC, sans altérer la sensibilité de l'ECG à dépister une pathologie.

Conclusion: Les critères ECG affinés que nous proposons ont le potentiel de diminuer la charge des faux positifs, en particulier chez les athlètes afro-caribéens.

Comparison of Electrocardiographic Criteria for the Detection of Cardiac Abnormalities in Elite Black and White Athletes

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Background—Recent efforts have focused on improving the specificity of the European Society of Cardiology (ESC) criteria for ECG interpretation in athletes. These criteria are derived predominantly from white athletes (WAs) and do not account for the effect of Afro-Caribbean ethnicity or novel research questioning the relevance of several isolated ECG patterns. We assessed the impact of the ESC criteria, the newly published Seattle criteria, and a group of proposed refined criteria in a large cohort of black athletes (BAs) and WAs.

Methods and Results—Between 2000 and 2012, 1208 BAs were evaluated with history, examination, 12-lead ECG, and further investigations as appropriate. ECGs were retrospectively analyzed according to the ESC recommendations, Seattle criteria, and proposed refined criteria which exclude several specific ECG patterns when present in isolation. All 3 criteria were also applied to 4297 WAs and 103 young athletes with hypertrophic cardiomyopathy. The ESC recommendations raised suspicion of a cardiac abnormality in 40.4% of BAs and 16.2% of WAs. The Seattle criteria reduced abnormal ECGs to 18.4% in BAs and 7.1% in WAs. The refined criteria further reduced abnormal ECGs to 11.5% in BAs and 5.3% in WAs. All 3 criteria identified 98.1% of athletes with hypertrophic cardiomyopathy. Compared with ESC recommendations, the refined criteria improved specificity from 40.3% to 84.2% in BAs and from 73.8% to 94.1% in WAs without compromising the sensitivity of the ECG in detecting pathology.

Conclusion—Refinement of current ECG screening criteria has the potential to significantly reduce the burden of false-positive ECGs in athletes, particularly BAs. (*Circulation*. 2014;129:1637-1649.)

Key Words: cardiomyopathies ■ echocardiography ■ electrocardiography ■ ethnic groups ■ exercise ■ hypertrophy ■ mass screening

Preparticipation screening for the early identification of young athletes at risk of exercise-related sudden cardiac death (SCD) is recommended by a growing number of sporting bodies and scientific organizations worldwide.¹⁻³ Whereas evidence from Italy suggests that ECG-based screening is effective at detecting athletes with potentially serious cardiac disorders,^{4,5} justifiable concerns remain related to high false-positive rates arising from the overlap between physiological ECG patterns and those reflecting cardiac pathology.⁶⁻⁸

Editorial see p 1626 Clinical Perspective on p 1649

The 2010 European Society of Cardiology (ESC) recommendations for ECG interpretation in athletes have attempted to facilitate the differentiation between physiological ECG patterns (group 1) and those indicative of cardiac disease (group

2).⁹ Although such categorization has improved specificity,^{8,10} false-positive rates between 10% and 20% have invariably prompted calls for further refinement.¹¹ A recent collaboration between international experts culminated in the Seattle criteria,¹² which have improved specificity in some populations.¹³

New data based on large athlete cohorts from our group have revealed several isolated ECG patterns to have a low diagnostic yield for cardiac disease, questioning their relevance as markers of pathology in elite athletes.^{14,15} Current guidelines in practice are consensus based and do not fully incorporate such scientific observations in their recommendations. Furthermore, they are derived almost exclusively from unselected white athletes (WAs)¹⁶ and have not been evaluated in large cohorts of elite athletes of African/Afro-Caribbean origin (black athletes; BAs). The paucity of ECG interpretation criteria in BAs is of concern, given that they most

Received September 9, 2013; accepted January 28, 2014.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.113.006179

frequently exhibit profound ECG alterations^{7,17–21} that overlap with primary cardiomyopathies, which magnifies their risk of an erroneous diagnosis.

This study assessed the performance of the ESC and Seattle criteria in large cohorts of highly trained BAs and WAs compared with proposed refined criteria (Figure 1A) that incorporate new research findings and the effect of black ethnicity.^{7,14,15,17,19,20} To determine their sensitivity for the detection of hypertrophic cardiomyopathy (HCM), all 3 criteria were applied to a well-characterized cohort of young, asymptomatic athletes with HCM.

Methods

Setting

The United Kingdom does not support a state-sponsored cardiac screening program in athletes. However, the charitable organization Cardiac Risk in the Young has an established cardiac screening program for young individuals that also serves many professional sporting organizations, including the English Institute of Sport, Lawn Tennis Association, Aviva Premiership Rugby, and Football Association.²² Up to 1000 athletes from numerous regional or national sporting squads are assessed annually. Most preliminary evaluations, including ECG and echocardiography, are performed at training centers through a mobile investigations unit and supervised

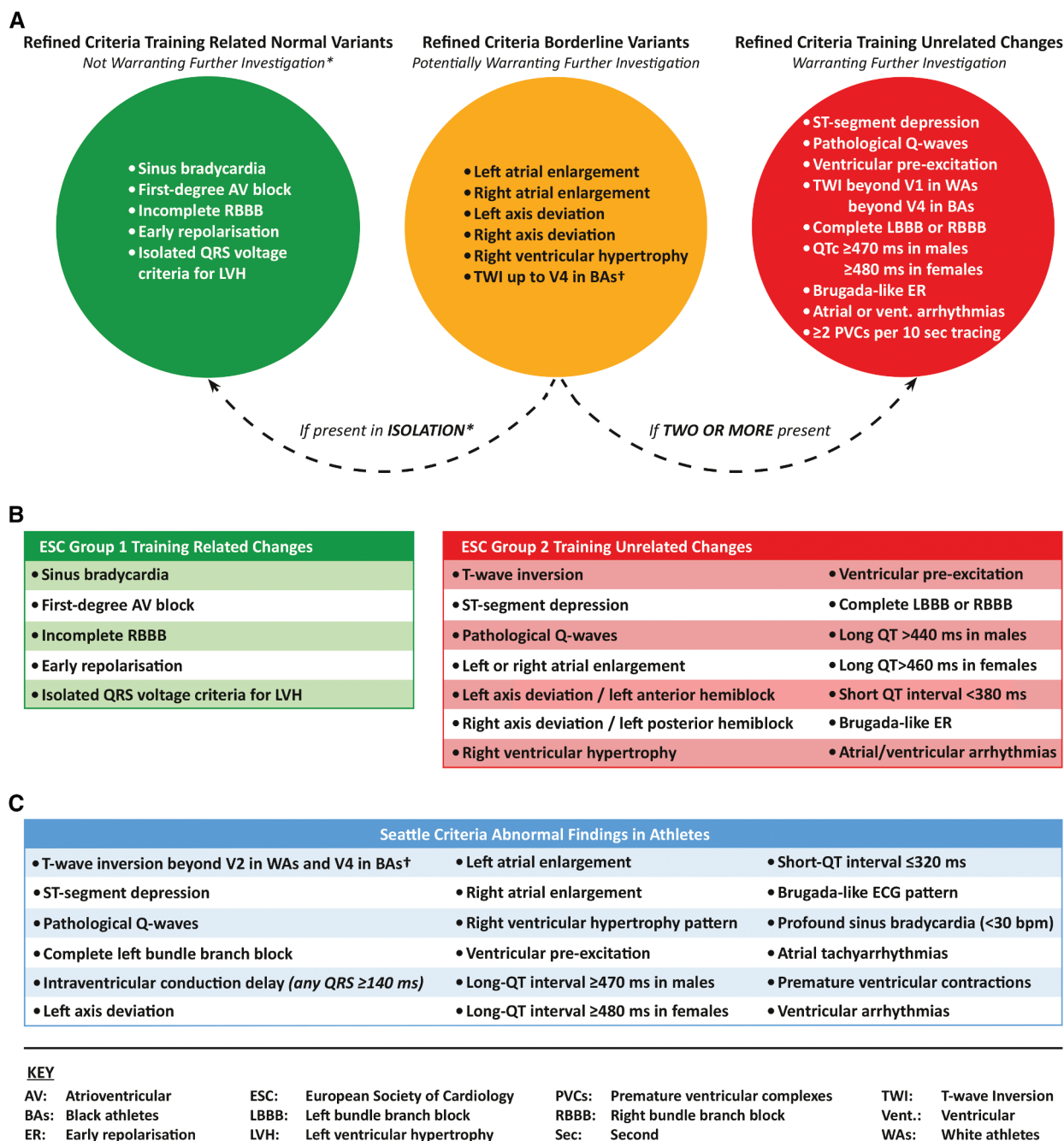


Figure 1. The definition of an abnormal ECG using the (A) refined criteria, (B) European Society of Cardiology (ESC) recommendations,⁹ and (C) Seattle criteria.¹²

by the principal investigator (S.S.). Most athletes with abnormal findings are investigated further in a dedicated Inherited Cardiac Diseases and Sports Cardiology Unit at St. George's Hospital.⁷

Elite Athletes

Between 2000 and 2012, 1208 elite BAs and 4297 elite WAs 14 to 35 years of age were evaluated with a health questionnaire, cardiovascular examination, and 12-lead ECG. An athlete was considered elite if competing regularly at the regional, national, or international level and exercising for ≥ 6 h/wk. Ethnicity was self-assigned. Individuals with concerning symptoms, family history of cardiomyopathy or premature (≤ 40 years) SCD, a cardiac murmur, or an abnormal ECG were assessed with 2-dimensional echocardiography and further investigations as necessary. A large proportion of elite athletes competing at the national or international level underwent 2-dimensional echocardiography as standard in accordance with the screening protocol required by their sporting organizations.

Investigations in Elite Athletes

Electrocardiography

ECG was performed with standard 12-lead positions using a GE Marquette Hellige (Milwaukee, WI) or Philips Pagewriter Trim III (Bothel, WA) as described elsewhere.¹⁷

Echocardiography

Two-dimensional echocardiography was performed with a GE Vivid I (Tirat, Israel), Philips Sonos 7500, Philips iE33, or Philips CPX50. Standard views were obtained, and cavity and wall thickness measurements were performed using established guidelines.²³ Pulsed Doppler recordings were performed at the distal margins of the mitral valve leaflets for early (E) and late (A) diastolic velocities. Tissue Doppler imaging of septal and lateral mitral annular movement was recorded from the apical 4-chamber views to obtain early (E') and late (A') diastolic peak velocities.²⁴ The ratios of transmitral flow velocity to the septal (E/E'sept) and lateral (E/E'lat) annular velocities were averaged (E/E'average) to provide an index of diastolic function.²⁵ Left ventricular ejection fraction was calculated from left ventricular volumes with the Simpson rule.²³

Further Investigations

Requirement for further investigations was determined by symptomatic status, relevant family history, abnormal examination, and results of the ECG or echocardiogram. These included a maximal exercise tolerance test, 24-hour Holter monitor, and cardiac magnetic resonance imaging scan, as described previously.⁷

ECG Interpretation

The first comprehensive recommendations for interpretation of a young athlete's ECG were published by the ESC in 2005 and modified in 2010 to improve specificity. In 2012, an international panel adjourned in Seattle to provide yet another revision to facilitate the development of universally accepted guidelines for ECG interpretation in young athletes that may also be applicable to BAs. Between 2000 and 2010, our own practice for ECG interpretation in athletes was similar to the 2010 ESC recommendations and was associated with an unacceptably high false-positive rate.

Refined ECG Criteria

Between 2010 and 2012, we reassessed our practice of ECG interpretation in athletes more critically. On the basis of our long-standing experience of evaluating several thousand athletes and in line with recent consensus documents and research findings,^{7,12,14,15,17,19,20,26} we identified certain ECG anomalies (borderline variants; Figure 1A) currently included in the group 2 category of the ESC recommendations and some deemed abnormal by the Seattle criteria that we would now consider normal variants in asymptomatic athletes without a relevant family history or abnormal cardiac examination. Specifically, we would not recommend further investigation of athletes with any one of the following ECG patterns when present either in isolation or

in association with recognized training-related ECG changes: (1) left atrial enlargement, (2) right atrial enlargement, (3) left axis deviation, (4) right axis deviation, and (5) Sokolow-Lyon voltage criteria for right ventricular hypertrophy. On the basis of our experience²⁷ and in conjunction with the Bethesda guidelines²⁸ and more recent Seattle criteria,¹² we have increased the cutoff for an abnormal corrected QT interval (QTc) to 470 milliseconds in male and 480 milliseconds in female athletes. Finally, consistent with previous publications from our group,^{7,17,19,20} we no longer investigate asymptomatic BAs with T-wave inversion preceded by convex ST-segment elevation confined to V_1 through V_4 , a practice also adopted by the recent Seattle criteria.¹² Conversely, the presence of ≥ 2 of these 6 patterns in combination or in association with other group 2 ESC changes would be a requirement for further investigation. The refined criteria are illustrated in Figure 1A. Definitions of specific ECG patterns used in all 3 criteria are provided in Table 1.

Retrospective ECG Analysis

The ECGs of all 5505 elite athletes were analyzed retrospectively using the ESC recommendations and Seattle criteria, with specific attention given to the presence of abnormalities necessitating further investigation (ESC group 2 changes⁹ [Figure 1B] or Seattle criteria abnormal ECG findings in athletes¹² [Figure 1C]). We also applied the refined criteria retrospectively to our entire cohort of athletes. During ECG analysis, readers were blinded to pathological findings in all athletes.

Athletes With HCM

We applied the ESC recommendations, Seattle criteria, and refined criteria to a well-characterized cohort of 103 consecutive young athletes with HCM assessed in 4 dedicated cardiomyopathy clinics in London (United Kingdom) and the French Institute of Health and Medical Research in Rennes (France). All individuals were between 14 and 35 years of age, were asymptomatic, and exercised for a minimum of 4 h/wk at the time of presentation, enabling the performance of ECG criteria in identifying HCM to be assessed in a group comparable to that encountered during preparticipation evaluation. The initial 12-lead ECG obtained at the time of the first evaluation was used for analysis. Athletes were diagnosed with HCM after investigation for abnormalities identified through preparticipation evaluation, after cascade screening of family members of an individual affected with HCM, or after referral for a specialist opinion from another center.

HCM was diagnosed on the basis of left ventricular hypertrophy (LVH) ≥ 15 mm in any myocardial segment, as assessed on echocardiography or cardiac magnetic resonance imaging, in the presence of a nondilated left ventricle and the absence of another cardiac disorder or systemic condition capable of producing the same magnitude of LVH.²⁹ In cases of mild LVH (<15 mm), HCM was diagnosed in the context of a combination of features,³⁰ including ECG repolarization anomalies, specifically ST-segment depression or marked T-wave inversion; unusual patterns of LVH; the presence of a small left ventricular cavity; identification of HCM in a first-degree relative; or a positive gene test.

Ethics Approval

Ethics approval was granted by the National Research Ethics Service, Essex 2 Research Ethics Committee in the United Kingdom, the French Ministry of Health and Youth in France, and Shafallah Medical Genetic Center in Qatar. Written consent was obtained from athletes ≥ 16 years of age and from a parent or guardian for those <16 years of age.

Statistical Analysis

Data were expressed as mean \pm SD or percentages as appropriate and analyzed with SPSS software, version 20 (Chicago, IL). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Group differences were tested with the Student *t* test or Mann-Whitney *U* test for normally and

Table 1. ECG Parameters Used to Define Various ECG Abnormalities in the European Society of Cardiology Recommendations, Seattle Criteria, and Refined Criteria

ECG Abnormality	European Society of Cardiology Recommendations ⁹	Seattle Criteria ¹²	Refined Criteria
Left atrial enlargement	Negative portion of the P wave in lead V ₁ ≥0.1 mV in depth and ≥40 ms in duration	Prolonged P wave duration of >120 ms in lead I or II with negative portion of the P wave ≥1 mm in depth and ≥40 ms in duration in lead V ₁	As ESC
Right atrial enlargement	P-wave amplitude ≥2.5 mm in lead II, III, or aVF	As ESC	As ESC
Left QRS axis deviation	−30° to −90°	As ESC	As ESC
Right QRS axis deviation	>115°	>120°	As ESC
Right ventricular hypertrophy	Sum of R wave in V ₁ and S wave in V ₅ or V ₆ ≥10.5 mm	Sum of R wave in V ₁ and S wave in V ₅ >10.5 mm and right axis deviation >120°	As ESC
Complete LBBB	QRS ≥120 ms, predominantly negative QRS complex in lead V ₁ (QS or rS), and upright monophasic R wave in leads I and V ₆	As ESC	As ESC
Complete RBBB	RSR' pattern in anterior precordial leads with QRS duration ≥120 ms	Not relevant	As ESC
Intraventricular conduction delay	Any QRS duration >120 ms including RBBB and LBBB	Any QRS duration ≥140 ms or complete LBBB	As ESC
Pathological Q-wave	>4 mm deep in any lead except III, aVR	>3 mm deep or >40 ms duration in ≥2 leads except III and aVR	≥40 ms in duration or ≥25% of the height of the ensuing R wave
Significant T-wave inversion	≥2 mm in ≥2 adjacent leads (deep) or "minor" in ≥2 leads	>1 mm in depth in ≥2 leads V ₂ –V ₆ , II and aVF, or I and aVL (excludes III, aVR, and V ₁)	As Seattle
ST-segment depression	≥0.5 mm deep in ≥2 leads	As ESC	As ESC
Ventricular preexcitation	PR interval <120 ms with or without delta wave	PR interval <120 ms with delta wave	As Seattle criteria

LBBB indicates left bundle-branch block; and RBBB, right bundle-branch block.

non-normally distributed variables, respectively. The χ^2 test was used to compare the proportion of positive ECGs in BAs versus WAs within each criterion, with significance defined as $P<0.05$ throughout. Positive agreement between the 3 criteria was determined using κ and c statistics.

The sensitivity and specificity for the screening process and 95% confidence intervals were calculated from the athletic population who underwent history, examination, ECG, and echocardiography as standard, using 2×2 contingency tables in GraphPad Prism software, version 6.01 (La Jolla, CA). Sensitivity was defined as the ability to detect any cardiac disorder in this cohort (serious or minor) through the screening procedures performed (history, examination, ECG, and echocardiography). A serious cardiac disorder was defined as one that has been implicated as a recognized cause of exercise-related SCD in young athletes. Specificity was defined as the ability to correctly identify athletes without a cardiac disorder in this cohort with the screening procedures performed. Echocardiography was used as the gold-standard test for the detection or exclusion of structural disease. Negative and positive predictive values were calculated on the basis of the definitions above.

Results

Athlete Demographics

The majority of BAs and WAs were male (85.8% and 76.8%, respectively). Overall, WAs were younger than BAs (19.3±5.4 versus 22.2±5.7 years; $P<0.001$). WAs and BAs had similar body surface areas (1.92±0.26 versus 1.92±0.21 m²; $P=0.7$), and all had a blood pressure of ≤140/90 mmHg. Athletes

competed in a total of 31 different sporting disciplines; the top 5 sports represented were soccer (26.2%), rugby (11.6%), athletics (11.1%), tennis (9.5%), and swimming (6.5%). WAs exercised for slightly more hours per week than BAs (16.3±7.5 versus 15.5±6.1 hours; $P<0.001$). Of the BAs, 56.4% were of West African origin, 26.5% Caribbean, 14.9% North African, and 4.8% East African; 4.6% were of mixed ethnicity, and 2.7% were from the Americas.

Characteristics of Athletes With HCM

The average age of athletes with HCM was 24.3±6.9 years (range, 14–35 years), and the majority (94.2%) were male. Athletes with HCM exercised for an average of 9.7±5.1 h/wk. A significant percentage of the total HCM cohort ($n=34$, 33.0%) were African/Afro-Caribbean. Further characteristics of athletes with HCM are provided in Table 2.

Nine athletes (8.7%) with HCM showed concentric LVH and wall thicknesses <15 mm, placing them in a diagnostic grey zone between athlete's heart and HCM. Of these, 7 were Afro-Caribbean. All 9 exhibited deep T-wave inversion extending into the inferolateral leads, 2 showed pathological Q waves, and 4 revealed resting ST-segment depression. The mean relative wall thickness in this group was 0.5±0.08. Four athletes exhibited late gadolinium enhancement on cardiac magnetic resonance imaging, and 3 had a family history of HCM or SCD.

Table 2. Characteristics of 103 Athletes With Hypertrophic Cardiomyopathy

Age at diagnosis, y	24.3±6.9
Male sex, %	94.2
African/Afro-Caribbean ethnicity, %	33.0
Blood pressure, mm Hg	123±12/73±11
Family history of hypertrophic cardiomyopathy/sudden cardiac death, %	29.2
Mode of diagnosis, %	
Preparticipation screening abnormal ECG	81.3
Family screening	16.7
Other	2.0
Echocardiographic characteristics	
Left atrial dimension, mm	38.1±6.6
Left ventricular cavity dimension in diastole, mm	47.3±5.9
Maximal left ventricular wall thickness, mm	15.5±2.9
Relative wall thickness	0.61±0.23
Left ventricular mass, g	255.1±76.9
Mitral inflow E wave, m/s	0.77±0.17
Mitral inflow A wave, m/s	0.47±0.11
E/A	1.78±0.55
E' lateral, m/s	0.12±0.03
E' septal, m/s	0.08±0.02
E/E' average	8.2±2.8
Resting systolic anterior motion of mitral valve leaflets, %	8.6
Resting left ventricular outflow tract gradient ≥30 mm Hg, %	3.4
Left ventricular ejection fraction, %	68.2±7.2
LVH pattern, %	
Apical	35.7
Septal	44.0
Concentric	15.5
Other	4.8
ECG characteristics, %	
Sinus bradycardia (heart rate <60 bpm)	52.4
LVH (Sokolow-Lyon criteria)	60.2
Romhilt-Estes score ≥4/≥5	88.3/68.9
Right ventricular hypertrophy (Sokolow-Lyon criteria)	10.7
Left atrial enlargement	37.9
Right atrial enlargement	18.4
Left axis deviation	7.8
Right axis deviation	1.9
Pathological Q waves	25.2
Inverted T waves	97.1
Deep	87.4
V ₁ -V ₄	2.0
Inferior leads	11.0
Lateral leads	87.0
ST-segment elevation	63.1
ST-segment depression	54.4

E/A indicates ratio of mitral inflow E and A waves; E/E', ratio of mitral inflow E wave to mitral annular tissue Doppler E'; and LVH, left ventricular hypertrophy.

Analysis of ECGs

Application of the ESC Recommendations and Seattle Criteria

The number of ECGs deemed abnormal with the use of the ESC recommendations and Seattle criteria is illustrated in Figure 2. Application of the ESC recommendations to our total athlete cohort resulted in 1183 athletes (21.5%) being designated as abnormal. BAs were 2.5 times more likely to exhibit an abnormal ECG compared with WAs (40.4% versus 16.2%; $P<0.0001$). The most prevalent ECG abnormalities in BAs were T-wave inversion (19.3%), right ventricular hypertrophy (10.7%), and left or right atrial enlargement (13.8%; Figure 3).

The Seattle criteria reduced the number of abnormal ECGs to 9.6% for the total athlete cohort. With the use of the Seattle criteria, BAs were 2.6 times more likely to exhibit an abnormal ECG compared with WAs (18.4% versus 7.1%; $P<0.0001$; Figure 2).

Refined Criteria

The refined criteria reduced the number of abnormal ECGs to 6.6% for the total athlete cohort. Compared with the ESC and Seattle criteria, the refined criteria were associated with a significant reduction in the number of abnormal ECGs in both BAs and WAs, to 11.5% and 5.3%, respectively ($P<0.0001$; Figure 2). Relative to the ESC recommendations, the refined criteria offered a 71.5% reduction in abnormal ECGs in BAs and a 67.3% reduction in WAs. In absolute terms, this represented an almost 3-fold greater reduction in abnormal ECGs in BAs compared with WAs (28.9% versus 10.9%, respectively). Relative to the Seattle criteria, the refined criteria offered a further 37.5% reduction in abnormal ECGs in BAs and a 25.4% reduction in WAs. On the basis of the refined criteria, the leading cause for an abnormal ECG in BAs remained T-wave inversion (Figure 3) in the inferior and lateral leads.

Comparison of Criteria for Agreement

Comparison of the 3 criteria for positive results in BAs and WAs revealed the strongest agreement between the Seattle and refined criteria, particularly in WAs (Table 3 and Figure 4). There was only fair to moderate agreement between the ESC recommendations and the refined and Seattle criteria for BAs and WAs.

Application of the ESC, Seattle, and Refined Criteria to Athletes With HCM

All 3 ECG criteria detected all but 2 athletes with HCM (1.9%) on the basis of ECG alone. Both athletes exhibited a normal ECG. The first individual was diagnosed after routine echocardiography as part of his preparticipation evaluation; the second was diagnosed after family screening for HCM (Table 4).

None of the athletes with HCM exhibited isolated atrial enlargement, axis deviation, or right ventricular hypertrophy on their ECGs. Similarly, none of the BAs with HCM showed isolated T-wave inversion in V₁ through V₄.

Identification of Pathology

Of the 3210 athletes (58.3%) who underwent echocardiography (2392 WAs [55.7%] and 818 BAs [67.7%]), 1183 (36.9%) had an ECG deemed abnormal (695 WAs and 488 BAs), 28 (0.9%) had symptoms, 24 (0.7%) had a cardiac murmur, and

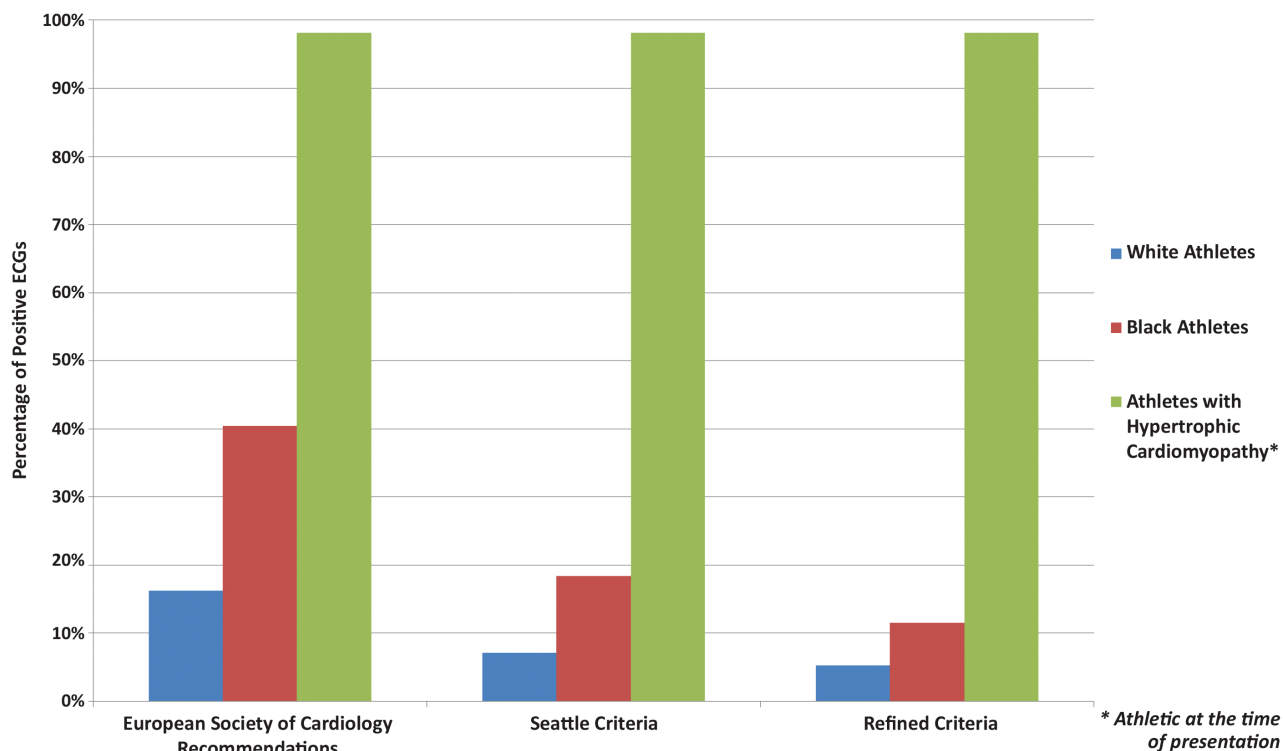
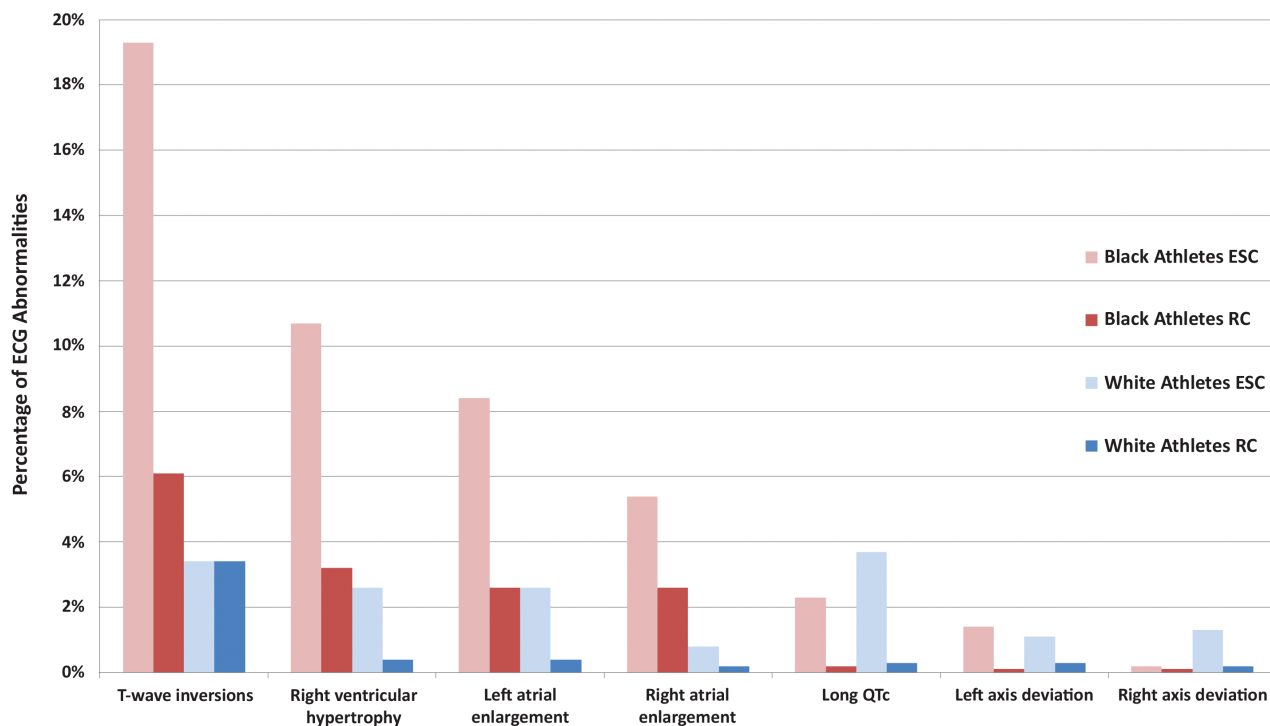


Figure 2. The number of positive ECGs produced by the 3 different ECG screening criteria.

20 (0.6%) had a significant family history. The remaining 1955 athletes (60.9%) underwent echocardiography despite normal preliminary investigations as a result of their club policy.

Of the 3210 athletes who underwent both ECG and echocardiography, 40 (1.25%) were diagnosed with a cardiac disorder. Specifically, 15 (0.47%) had a serious disorder: HCM



ECG Abnormalities by European Society of Cardiology (ESC) Recommendations and Refined Criteria (RC)

Figure 3. Prevalence of the 7 commonest abnormal ECG patterns in athletes, defined by the European Society of Cardiology recommendations and refined criteria.

Table 3. Agreement Between the 3 Criteria: Seattle, Refined, and European Society of Cardiology

	Positive ECGs, n	κ	95% Confidence Interval	c Statistic	95% Confidence Interval
Black athletes					
ESC positive, Seattle positive	222	0.50	0.45–0.55	0.78	0.76–0.80
Seattle positive, refined positive	139	0.73	0.68–0.79	0.93	0.92–0.95
ESC positive, refined positive	139	0.32	0.26–0.38	0.71	0.69–0.74
White athletes					
ESC positive, Seattle positive	305	0.57	0.53–0.61	0.91	0.90–0.92
Seattle positive, refined positive	228	0.85	0.81–0.88	0.98	0.98–0.99
ESC positive, refined positive	228	0.45	0.40–0.50	0.89	0.88–0.90

ESC indicates European Society of Cardiology.

(n=5), Wolff-Parkinson-White syndrome (n=5), long-QT syndrome (n=3), Brugada syndrome (n=1), and anomalous coronary artery origin (n=1). Twenty-five (0.78%) had a minor congenital/valvular abnormality: bicuspid aortic valve (n=10), mitral valve prolapse (n=7), atrial septal defect (n=3), ventricular septal defect (n=2), mild aortic regurgitation (n=1), mild pulmonary stenosis (n=1), and cor triatriatum (n=1; Figure 5).

Fourteen of the 15 athletes (93.3%) with a potentially serious cardiac disorder (including all 5 cases of HCM) were identified with ECG, and only 1 (6.7%) was detected on the basis of symptoms. Of the athletes with minor congenital abnormalities, 10 (40.0%) were identified on the basis of abnormal examination findings, and 15 (60.0%) were detected on routine

echocardiography in the setting of a normal history, examination, and ECG.

In contrast to the ability to detect sinister disorders, the ECG alone failed to identify all 25 individuals with minor congenital or valvular abnormalities, regardless of the ECG criteria used. The ECGs in these athletes revealed either normal or isolated group 1 changes.

Sensitivity and Specificity of the ESC Recommendations, Seattle Criteria, and Refined Criteria

Of the 3210 athletes who underwent echocardiography, 3087 (96.2%) were required to do so as part of their club's

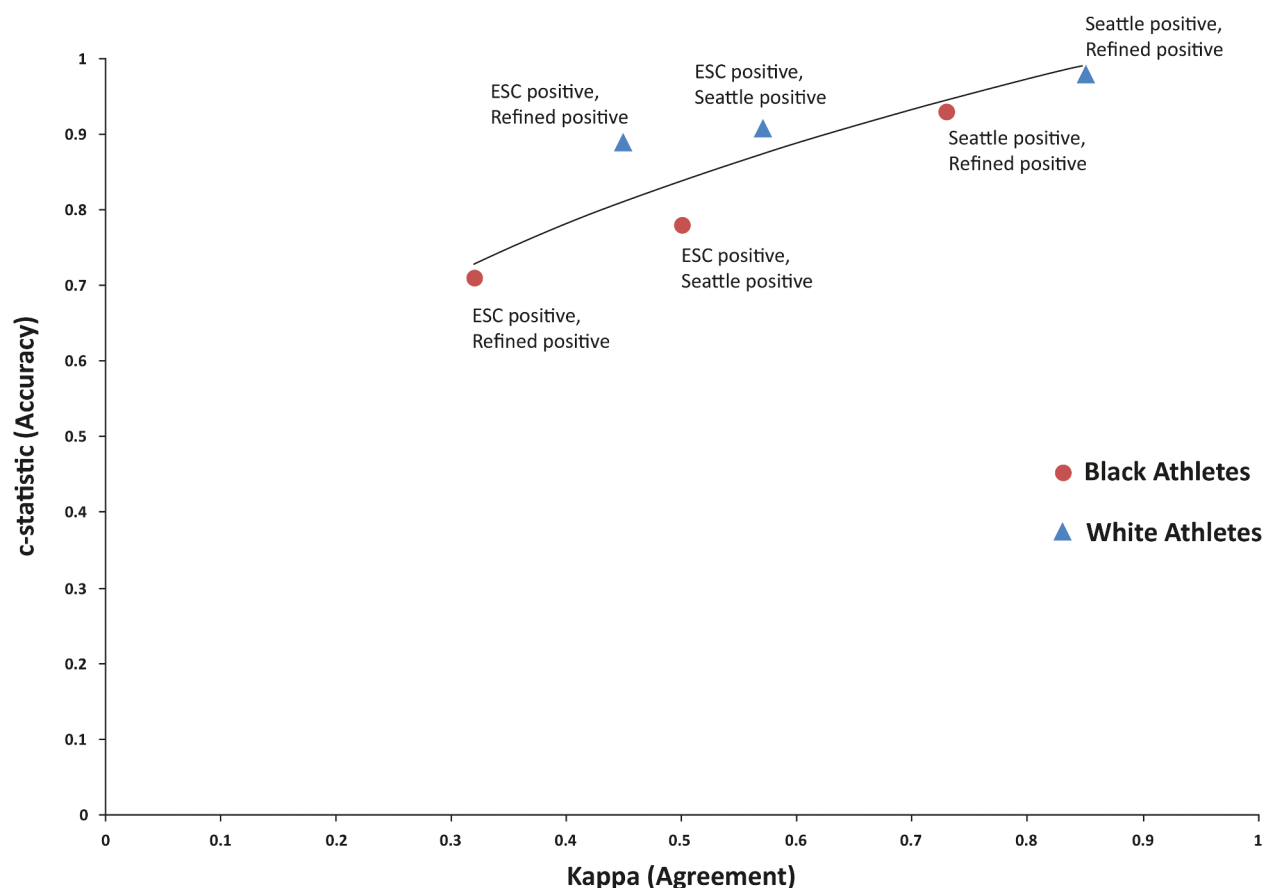


Figure 4. Correlation of κ and c statistic for each pair of criteria in white and black athletes (line represents trend of how these correlations are located). ESC indicates European Society of Cardiology.

Table 4. Characteristics of Athletes With Hypertrophic Cardiomyopathy and a Normal ECG

Age of Presentation, y	Sex	Ethnicity	Mode of Identification	Symptoms	Family History of Hypertrophic Cardiomyopathy	Examination Findings	ECG Findings	Maximum LVWT (Pattern), mm	Relative Wall Thickness	LGE on CMRI
18	Male	White	Preparticipation screening*	None	No	Nil	Nil	14† (Asymmetrical septal)	0.53	No
23	Male	White	Familial screening	None	Yes	Nil	Nil	14 (Asymmetrical septal)	0.42	No

CMRI indicates cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; and LVWT, left ventricular wall thickness.

*On routine echocardiography.

†No regression of left ventricular hypertrophy after detraining.

policy, regardless of clinical or ECG findings (805 BAs and 2282 WAs). This group contained all athletes diagnosed with pathology and was used to assess the effect of the refined criteria on the sensitivity and specificity of the overall screening process (Table 5). Compared with the ESC recommendations, the Seattle criteria were associated with a marked improvement in specificity for both BAs (40.3% to 79.3%) and WAs (73.8% to 92.1%). The refined criteria offered a further improvement in specificity, to 84.2% in BAs and 94.1% in WAs.

Sensitivity for all cardiac diseases remained 70.0% in BAs and 60.0% in WAs for all 3 criteria. After exclusion of minor congenital and valvular abnormalities, the sensitivity for all 3 criteria improved to 100% in both BAs and WAs without compromising specificity (ESC: 40.1% BAs and 73.5% WAs; Seattle: 79.3% BAs and 92.1% WAs; refined criteria: 84.2% BAs and 93.9% WAs; Table 6).

Interobserver Variability Between ECG Findings

There was excellent agreement with respect to ECG findings during reanalysis of a random selection of 1000 ECGs by the first and senior authors, translating to a κ (measurement of agreement) of 0.97 ($P<0.0001$).

Further Investigations and ECG Predictors of Cardiac Disease

A substantial number of athletes (3210, 58.3%) underwent additional investigations after the ECG (Figure 6). This group included 1955 asymptomatic athletes with normal/training-related ECG patterns who would have normally been cleared without additional tests but were required to have echocardiography as part of their club's policy. None of the 1955 athletes were diagnosed with a serious structural disorder.

Five hundred nineteen athletes (9.4%) were recommended for further investigations after ECG and echocardiography.

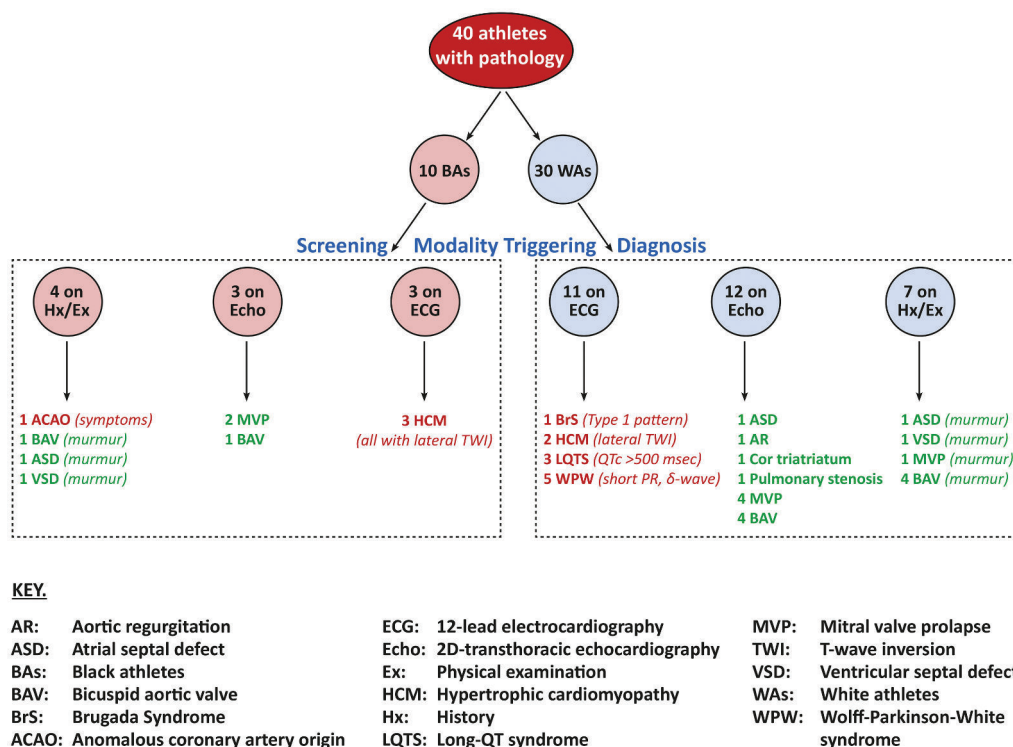


Figure 5. Number of athletes with pathology, characterized by ethnicity and screening modality triggering diagnosis. Green indicates minor congenital/valvular defects; and red, serious pathology.

Table 5. Sensitivity and Specificity of the Screening Process Using Different ECG Criteria to Detect Both Major and Minor Cardiac Abnormalities (95% Confidence Interval)

	Black Athletes (n=805)			White Athletes (n=2282)		
	European Society of Cardiology	Seattle Criteria	Refined Criteria	European Society of Cardiology	Seattle Criteria	Refined Criteria
Sensitivity, %	70.0 (34.8–93.3)	70.0 (34.8–93.3)	70.0 (34.8–93.3)	60.0 (40.6–77.3)	60.0– (40.6–77.3)	60.0 (40.6–77.3)
Specificity, %	40.3 (36.8–43.8)	79.3 (76.3–82.0)	84.2 (81.4–86.6)	73.8 (71.9–75.6)	92.1– (91.0–93.2)	94.1 (93.1–95.1)
Positive predictive value, %	1.5 (0.6–3.0)	4.1 (1.7–8.2)	5.3 (2.1–10.5)	3.0 (1.8–4.6)	9.2 (5.6–14.2)	12.0 (7.3–18.3)
Negative predictive value, %	99.1 (97.3–99.8)	99.5 (98.7–99.9)	99.6 (98.7–99.9)	99.3 (98.8–99.6)	99.4 (99.0–99.7)	99.4 (99.0–99.7)
False-positive rate, %	59.7	20.7	15.8	26.2	7.9	5.9
False-negative rate, %	30.0	30.0	30.0	40.0	40	40.0

Of these, 466 were advised to obtain a cardiac magnetic resonance imaging scan, exercise test, and Holter monitor to exclude a cardiomyopathy on the basis of marked ECG repolarization changes (n=389) or structural changes that placed them in the grey zone for cardiomyopathy (n=77), and 53 were advised an exercise test and Holter monitor on the basis of symptoms or family history (n=38) or a prolonged QT interval (n=15). Complete data were available in 454 athletes (87.5%), including all those with a prolonged QT interval, inferolateral T-wave inversion, and a wall thickness ≥ 13 mm (Figure 6).

Exercise testing facilitated the diagnosis of long-QT syndrome in 3 of 15 athletes (20%) with a prolonged QT interval. All 3 athletes revealed a QTc >500 milliseconds. Cardiac magnetic resonance imaging after echocardiography aided the diagnosis of a cardiomyopathy in only 2 of 401 athletes (0.5%) with marked repolarization changes or echocardiographic features of possible cardiomyopathy. Both athletes had HCM and exhibited lateral T-wave inversion. With respect to specific T-wave inversion patterns, lateral T-wave inversion was the only consistent finding in the 5 athletes with cardiomyopathy (all HCM) and had a positive predictive value of 22.2% in WAs, 8.3% in BAs, and 11.1% overall. In contrast,

T-wave inversion confined to the inferior leads did not predict any cardiomyopathy.

Discussion

This study compared the performance of current ESC and Seattle criteria for ECG interpretation in athletes compared with proposed refined criteria in a large cohort of elite BAs and WAs. All 3 criteria were also applied to a young group of asymptomatic athletes with HCM to assess their ability to detect a condition that accounts for a significant proportion of SCD in young athletes and often forms part of the differential diagnosis in athletic individuals with ECG anomalies or mild LVH on echocardiography.

ESC Recommendations and Seattle Criteria Versus Refined Criteria

The results indicate that although current ESC recommendations perform well in detecting HCM and excluding potentially sinister structural disease, they are associated with unacceptably high false-positive rates, particularly in BAs. On the basis of current ESC recommendations, almost 1 in 2 BAs and almost 1 in 5 WAs exhibit ECG patterns warranting further evaluation (Figure 2). These findings are highly problematic,

Table 6. Sensitivity and Specificity of the Screening Process Using Different ECG Criteria to Detect Major Cardiac Abnormalities Only (95% Confidence Interval)

	Black Athletes (n=805)			White Athletes (n=2282)		
	European Society of Cardiology	Seattle Criteria	Refined Criteria	European Society of Cardiology	Seattle Criteria	Refined Criteria
Sensitivity, %	100 (39.8–100)	100 (39.8–100)	100 (39.8–100)	100 (71.5–100)	100 (71.5–100)	100 (71.5–100)
Specificity, %	40.1 (36.7–43.6)	79.3 (76.3–82.0)	84.2 (81.4–86.6)	73.5 (71.7–75.3)	92.1 (91.0–93.2)	93.9 (92.9–94.9)
Positive predictive value, %	0.8 (0.2–2.1)	2.4 (0.6–5.9)	3.1 (0.8–7.7)	1.8 (0.9–3.2)	5.9 (3.0–10.2)	7.4 (3.8–12.9)
Negative predictive value, %	100 (98.9–100)	100 (99.4–100.0)	100 (99.5–100)	100 (99.8–100)	100 (99.8–100)	100 (99.8–100)
False-positive rate, %	59.9	20.7	15.8	26.5	7.9	6.1
False-negative rate, %	0.0	0.0	0.0	0.0	0.0	0.0

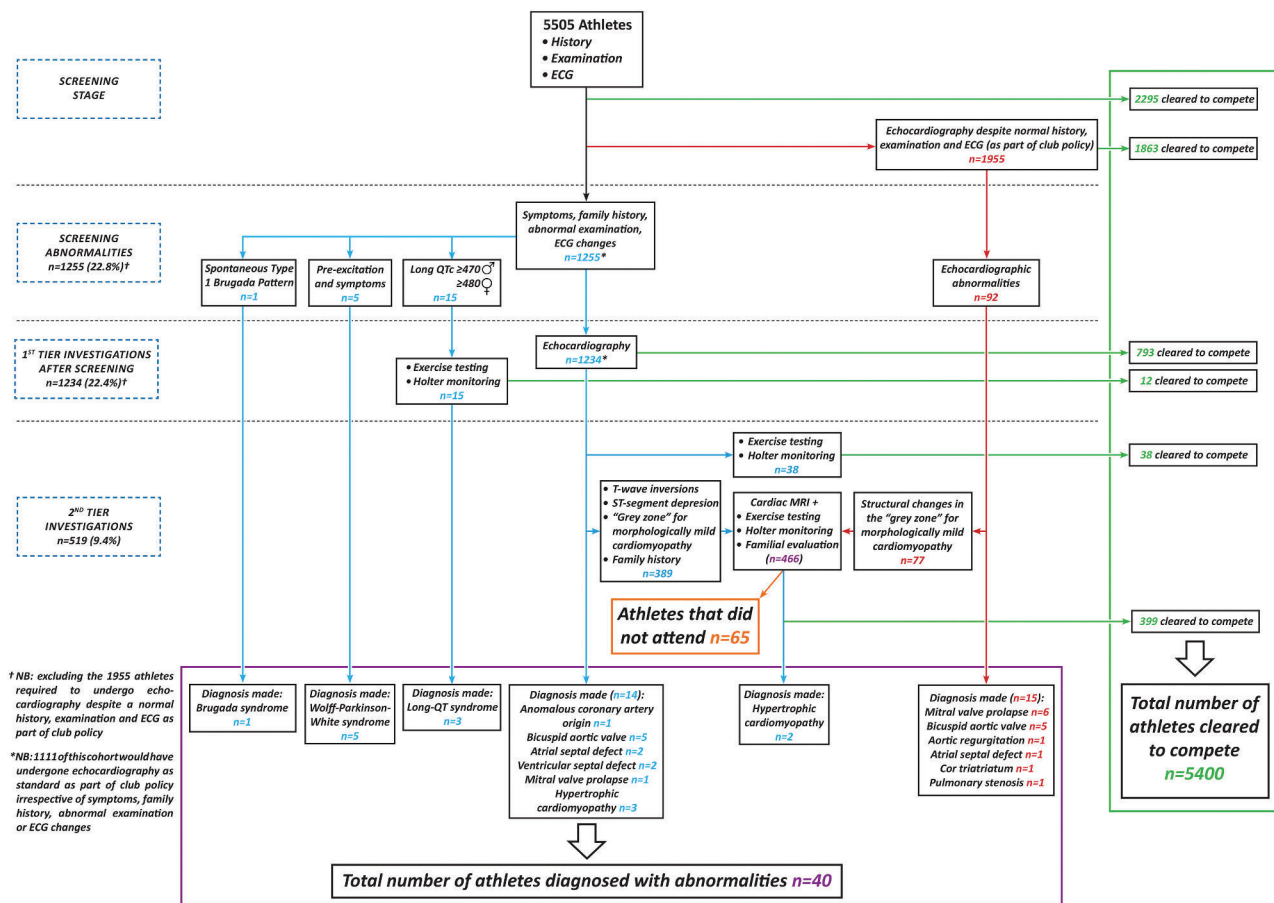


Figure 6. Diagnostic algorithm for further investigations after initial screening that led to an ultimate cardiac diagnosis in our athlete cohort. The total numbers of athletes cleared are shown on the **right** (green box), and the total numbers of athletes diagnosed with a cardiac condition are shown at the **bottom** (purple box). Sixty-five athletes requiring second-tier investigations failed to attend (orange box).

particularly in countries accommodating large populations of BAs, including the United Kingdom and the United States.

In agreement with a recent analysis,¹³ the Seattle criteria perform well in identifying sinister disease and are associated with a significant improvement in specificity in WAs. However, despite accounting for anterior T-wave inversion (V_1 – V_4) as a normal ethnic variant,^{7,14,15,17,19,20} almost one fifth of BAs continue to exhibit abnormal ECG patterns (Figure 2) after application of the Seattle criteria, primarily as a result of the presence of isolated voltage criteria for atrial enlargement and left axis deviation. Such ECG patterns also appear highly relevant in WAs and account for a high proportion of abnormal ECGs (Figures 2 and 3). We have recently demonstrated that the presence of any one of these ECG patterns, either in isolation or in combination with recognized training-related ECG patterns, correlates poorly with underlying cardiac disorders in asymptomatic elite athletes.^{14,15} By excluding these ECG patterns from the abnormal category, the refined criteria result in a significant improvement in specificity in athletes of both ethnicities while maintaining sensitivity (Tables 5 and 6).

The refined criteria have the most impressive impact on the BA population, in whom the false-positive ECG rate is decreased by >70% compared with current ESC recommendations. Indeed, application of the refined criteria results in

a lower positive ECG rate in BAs (11.5%) than is presently observed in WAs (16.2%) with the ESC recommendations (Figure 2). Importantly, the refined criteria also have a significant impact on WAs, reducing the false-positive ECG rate to a far more acceptable level of 5.9%. In the current financial climate, the impact on resources and cost savings inherent in such refinement is difficult to ignore.

Clinical Implications

Identification of Pathology

The refined criteria identified all elite athletes with potentially sinister pathology and the majority of athletes (98.1%) with HCM. These observations are particularly important for BAs, who reveal a higher relative risk of exercise-related SCD resulting from HCM.³¹

Regardless of the criteria used, the ECG was poor at identifying minor congenital abnormalities and valvular heart disease, some of which may theoretically degenerate more rapidly in individuals exercising at high intensities. Inclusion of clinical examination, which is usual practice in both the American Heart Association and ESC screening protocols, improved the detection rate to >40%, highlighting the importance of this aspect of preparticipation cardiovascular evaluation.

Future Directions

Despite the ongoing debate between the American Heart Association and ESC concerning routine use of 12-lead ECGs, the vast majority of professional sporting organizations in the United States³² and Europe incorporate an ECG in their screening protocols. Therefore a significant number of athletes, including BAs who make up almost 70% of individuals participating in certain sports in the United States, continue to be evaluated with ECG before clearance to compete. The high false-positive rates observed in BAs with current ECG screening criteria support concerns raised by the American Heart Association. With this consideration in mind, the best alternative is to strive toward an improvement in screening specificity through a better understanding of benign versus abnormal ECG patterns, coupled with appropriate training and education of physicians in the correct interpretation of an athlete's ECG.^{12,33}

The ESC recommendations are unfavorable to BAs. The recently published Seattle criteria¹² perform better by incorporating a growing body of scientific evidence^{7,17,19,20} relating to electric remodeling in athletes of Afro-Caribbean ethnicity. Further refinement of current ECG criteria as demonstrated above improves the unfavorable situation in BAs without compromising the detection of HCM. We have previously reported that T-wave inversion confined to V_1 through V_4 in BAs is a normal variant.^{7,17,19,20} This study revealed that T-wave inversion confined to the inferior leads failed to predict cardiomyopathy

in BAs (Figure 7). Therefore, it is possible that exclusion of this particular repolarization pattern in BAs in the future may reduce the false-positive rate to <10%.

Study Limitations

In this study, echocardiographic data were not available in all individuals; therefore, we may have underestimated the prevalence of some minor abnormalities. However, a large number of athletes (3210) underwent both ECG and echocardiography, which enabled robust conclusions on the role of ECG in identifying diseases implicated in exercise-related SCD. Given that many athletes with a normal ECG received only 1 echocardiogram, we cannot comment accurately on the false-negative results because some individuals may develop HCM at a later date. Although 98% of our athletes with HCM exhibited an abnormal ECG, we recognize the heterogeneity of HCM and that a small proportion may reveal normal ECGs or one of the aforementioned isolated ECG patterns that we would now consider as normal variants. Finally, the study was conducted in elite athletes; therefore, the applicability and comparisons of the refined criteria with the ESC recommendations and the Seattle criteria in nonelite athletes should be an area for further study.

Conclusions

Application of the proposed refined criteria significantly reduces the number of false-positive ECGs in both elite BAs

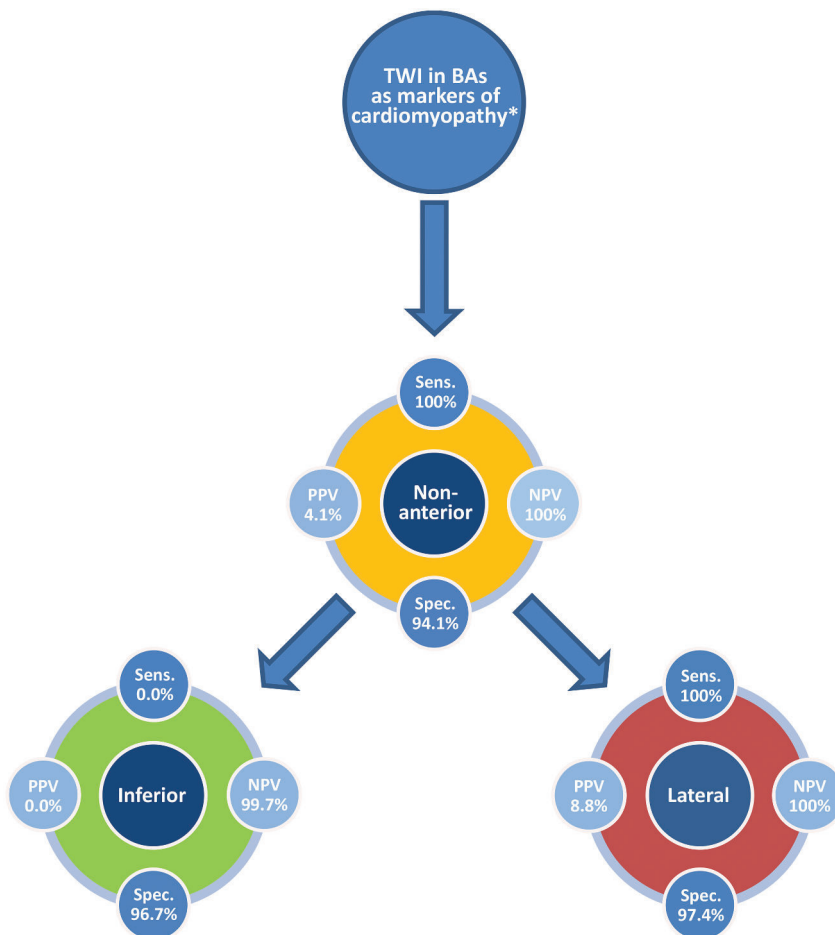


Figure 7. Sensitivity, specificity, and predictive values of T-wave inversion for cardiomyopathy in black athletes. *The only cardiomyopathy diagnosed in our athlete cohort was hypertrophic cardiomyopathy. BAs indicates black athletes; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; and TWI, T-wave inversion.

and WAs without compromising sensitivity. Coupled with appropriate training of physicians in ECG interpretation, such refinement of ECG screening criteria would minimize the risk of an erroneous diagnosis in BAs and lead to substantial savings from unnecessary investigations in both cohorts. The results from this preliminary study require further evaluation and confirmation by other centers. It is our aspiration that the data will provide an important evidence base for revising existing guidelines^{9,12} in the future.

Acknowledgments

We thank Cardiac Risk in the Young for providing the portable echocardiography equipment and ECG machines used for the study in the United Kingdom.

Sources of Funding

Studies on French athletes were supported by grants from the Club des Cardiologues du Sport and from the French Ministry of Health and Sport.

Disclosures

Drs Sheikh, Papadakis, Ghani, Zaidi, and Gati were funded by research grants from Cardiac Risk in the Young. Dr Sharma has been a coapplicant on previous grants from Cardiac Risk in the Young to study BAs. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Despite efforts to improve the specificity of ECG screening criteria in athletes, the issue of high false-positive rates is concerning. Athletes of African/Afro-Caribbean origin (black athletes; BAs) exhibit more profound electric changes compared with white athletes (WAs) and may be more susceptible to false-positive results and erroneous disqualification. The established 2010 European Society of Cardiology recommendations for ECG interpretation in athletes are derived exclusively from WAs and have not been tested in BAs. This study reports the performance of current ECG interpretation criteria in elite BAs and WAs compared with proposed “refined criteria,” which incorporate new research findings on benign ECG patterns in athletes and the effect of black ethnicity. The European Society of Cardiology recommendations, the more recent Seattle criteria, and the refined criteria were tested in 1208 BAs and 4297 WAs. All 3 criteria were applied to 103 young, asymptomatic athletes with hypertrophic cardiomyopathy. The European Society of Cardiology recommendations resulted in 40.4% BAs and 16.2% WAs exhibiting a positive ECG that would require investigation. The Seattle criteria reduced the number of positive ECGs to 18.4% in BAs and 7.1% in WAs. The refined criteria produced the greatest reduction, to 11.5% in BAs and 5.3% in WAs. All 3 criteria maintained 98% sensitivity to detect hypertrophic cardiomyopathy. Incorporation of the refined criteria into future ECG interpretation guidelines in athletes will reduce the burden of false-positive results in both WAs and BAs. The 71% reduction in positive ECGs in BAs compared with European Society of Cardiology recommendations has huge implications in countries accommodating a large population of BAs.

1.2.Intérêt de l'IRM en cas d'ondes T négatives chez l'athlète

Les résultats de l'étude précédente ont démontré qu'un certain nombre de modifications ECG, notamment la présence d'ondes T négatives, ne peuvent pas être considérées comme physiologiques.

Il est indispensable de déterminer quel bilan réaliser lorsque l'on détecte ce type d'anomalie ECG lors de la visite de non contre-indication à la pratique du sport en compétition. Une précédente étude avait déjà validé la nécessité de réaliser des examens complémentaires dans cette situation ²⁸ et avait démontré que cette anomalie électrique permettait le plus souvent de dépister des CMH. Néanmoins la nature du bilan n'avait pas été codifiée. L'une des questions principales était de savoir si l'IRM devait être incluse dans l'algorithme diagnostique, ou si l'échocardiographie était une technique suffisante pour dépister toutes les pathologies chez l'athlète avec ondes T négatives pathologiques.

Apport du candidat dans ce travail

Afin d'inclure prospectivement 155 athlètes avec ondes T négatives pathologiques, ce travail a nécessité la collaboration de nombreux centres français (via le Club des Cardiologues du Sport) et étrangers (le Qatar Orthopaedic and Sports Medicine Hospital, et le Centre for Cardiovascular Magnetic Resonance, Blackrock Clinic, Dublin).

Mon apport dans ce travail a été l'inclusion d'une grande part des athlètes, la relecture de l'ensemble des données et la rédaction du manuscrit.

RESUME

Objectifs: Les ondes T négatives (-) pathologiques sont rarement observées chez l'athlète alors qu'elles sont fréquemment observées chez les patients atteints de cardiopathie. Toutes les recommandations d'analyse de l'ECG chez l'athlète indiquent que la présence d'ondes T- chez l'athlète (hormis en aVR, III, V1 et V1–V4 si associée à une surélévation du segment ST en dôme chez l'athlète afro-caribéen asymptomatique) ne peut pas être considérée comme une adaptation physiologique. L'objectif de cette étude prospective était de déterminer la prévalence de cardiopathie chez les athlètes avec ondes T- et d'examiner la valeur ajoutée diagnostique de l'IRM dans cette population.

Méthodes et résultats: Les athlètes avec ondes T- (n=155) étaient évalués par un examen clinique, un ECG, une échocardiographie, un test d'effort, un Holter ECG/24h et une IRM cardiaque. Une cardiopathie a été dépistée chez 44.5% des athlètes, la CMH étant la principale pathologie retrouvée (81%). L'échocardiographie était anormale dans 53.6% des cas positifs, l'IRM cardiaque a permis d'identifier 24 autres athlètes avec cardiopathie. Au cours du suivi, 5 athlètes (7.2%) considérés comme normaux lors de l'évaluation initiale ont développé une cardiomyopathie. Une histoire familiale de mort subite et un sous décalage du segment ST associé aux ondes T- étaient prédictifs d'une cardiopathie.

Conclusion: La présence d'ondes T- doit être considérée comme pathologique sauf indication contraire au terme d'un bilan exhaustif. En effet, les ondes T- sont en lien avec une cardiopathie chez 45% des athlètes. Même si l'échocardiographie a été capable d'identifier une pathologie dans la moitié des cas, une IRM cardiaque doit être systématiquement réalisée chez les athlètes avec ondes T- et échocardiographie normale. En cas de bilan normal, l'athlète peut pratiquer le sport en compétition sous réserve d'un suivi annuel.

Recognition and Significance of Pathological T-Wave Inversions in Athletes

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Background—Pathological T-wave inversion (PTWI) is rarely observed on the ECG of healthy athletes, whereas it is common in patients with certain cardiac diseases. All ECG interpretation guidelines for use within athletes state that PTWI (except in leads aVR, III and V1 and in V1–V4 when preceded by domed ST segment in asymptomatic Afro-Caribbean athletes only) cannot be considered a physiological adaptation. The aims of the present study were to prospectively determine the prevalence of cardiac pathology in athletes presenting with PTWI, and to examine the efficacy of cardiac magnetic resonance in the work-up battery of further examinations.

Methods and Results—Athletes presenting with PTWI (n=155) were investigated with clinical examination, ECG, echocardiography, exercise testing, 24h Holter ECG, and cardiac magnetic resonance. Cardiac disease was established in 44.5% of athletes, with hypertrophic cardiomyopathy (81%) the most common pathology. Echocardiography was abnormal in 53.6% of positive cases, and cardiac magnetic resonance identified a further 24 athletes with disease. Five athletes (7.2%) considered normal on initial presentation subsequently expressed pathology during follow-up. Familial history of sudden cardiac death and ST-segment depression associated with PTWI were predictive of cardiac disease.

Conclusions—PTWI should be considered pathological in all cases until proven otherwise, because it was associated with cardiac pathology in 45% of athletes. Despite echocardiography identifying pathology in half of these cases, cardiac magnetic resonance must be considered routine in athletes presenting with PTWI with normal echocardiography. Although exclusion from competitive sport is not warranted in the presence of normal secondary examinations, annual follow-up is essential to ascertain possible disease expression. (*Circulation*. 2015;131:165-173. DOI: 10.1161/CIRCULATIONAHA.114.011038.)

Key Words: arrhythmogenic right ventricular cardiomyopathy ■ athletes ■ cardiomyopathy, hypertrophic

Intense physical training may induce electric and myocardial adaptations that are collectively referred to as the athlete's heart.^{1,2} Although the majority of these are physiological and distinct from heart disease, some ECG parameters observed in a minority of athletes present diagnostic conundrums, which are suggestive of pathology. A resting 12-lead ECG is recommended by the European Society of Cardiology³ as part of the preparticipation evaluation for athletes before competitive sport. Several ECG interpretation guidelines have been proposed for use within athletes,^{2,4} with all underlining that marked pathological T-wave inversion (PTWI) is abnormal and is unrelated to physiological adaptation induced through physical activity.^{1,2,4,5} PTWI has to be differentiated from the physiological T-wave inversion (T-wave inversion in leads aVR, III, and V1 and in V1–V4 when preceded by domed

ST segments in asymptomatic Afro-Caribbean athletes only).⁶ This pattern has also been reported as a normal variant pattern of repolarization in Afro-Caribbean athletes and is sometimes referred to as Juvenile Pattern.^{7,8}

Editorial see p 128 Clinical Perspective on p 173

PTWIs are observed in several diseases associated with sudden cardiac death (SCD) in athletes—hypertrophic cardiomyopathy (HCM),^{3,9,10} dilated cardiomyopathy (DCM), left ventricular noncompaction (LVNC),^{1,2,4,8} arrhythmogenic right ventricular cardiomyopathy (ARVC),^{3,11} and myocarditis.^{2,4,12} Accordingly, athletes presenting with these diseases are at risk of SCD and are usually excluded for competitive and intensive sport.^{2,4,5,13} Thus, the management of an athlete presenting with PTWI is

Received May 12, 2014; accepted October 10, 2014.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.114.011038

an extremely challenging issue for the sports cardiologist for 2 reasons^{9,10,14}—first because of the high association between PTWI and cardiac disease, and second because the ECG may be the first and only sign of pathology without actual phenotypic manifestations of disease on secondary investigations.

To plan optimal management and treatment strategies for athletes with PTWI, we and others have proposed that alongside personal symptoms, family history, physical examination, and ECG, secondary investigations should also include transthoracic echocardiography (TTE), maximal exercise testing, 24h Holter ECG, and late gadolinium enhanced cardiovascular MRI (CMR).¹⁴ Although TTE is routine and easily available, it is limited in its inability to accurately define processes that are occurring at the myocardial tissue level.¹⁴ In contrast, CMR imaging allows definition of abnormal processes occurring at the tissue level, including myocardial edema, fatty infiltration, and importantly, myocardial fibrosis.¹⁵ CMR also allows for imaging of myocardial regions not clearly seen on echocardiography such as the left ventricular (LV) anterolateral free wall and the LV apex.

Although these series of secondary investigations have been recommended,¹⁴ to our knowledge no study has evaluated the efficacy of these examinations in a large cohort of well-trained athletes presenting with PTWI. The aim of this investigation was to (1) prospectively determine the prevalence of cardiac pathology in athletes presenting with PTWI, and (2) examine the efficacy of including CMR in the battery of further examinations.

Methods

Population

Between December 2008 and April 2013, 6372 competitive athletes were referred for precompetitive sporting evaluation (4139 white, 1266 Afro-Caribbean, and 321 West-Asian male athletes and 398 white and 248 Afro-Caribbean female athletes) in a multicenter (n=8) prospective observational study. A total of 155 athletes presented with PTWI and were included in this study. The study was approved by the hospital ethics committee and conducted in accordance with the Declaration of Helsinki. All participants gave informed consent.

Inclusion Criteria

Sole inclusion criteria was any asymptomatic athlete with marked PTWI (≥ 2 mm) on a resting 12-Lead ECG in ≥ 2 leads (Figure 1). Athletes presenting with physiological TWI in leads III, aVR, and V1, and in V1 through V4 when TWI was preceded by convexed/

domed ST segment in Afro-Caribbean athletes only were not included (Figure 2).^{4,6,16}

Exclusion Criteria

Exclusion criteria consisted of any personal history of a disease known to adversely affect ECG repolarization patterns, personal symptoms that suggested coronary disease, drug use that may alter ECG repolarization patterns, and known electrolyte disturbance. Furthermore, athletes were excluded if presenting with other ECG patterns suggestive of cardiovascular disease.

Cardiovascular Evaluation

Clinical Examination

Family history (history of cardiomyopathy or sudden death in a first-degree relative <55 years of age), personal symptoms (palpitations, syncope or dizziness, chest pain, exercise related abnormal shortness of breath or fatigue, signs of a recent [≤ 6 weeks] infectious event, training level), and a physical examination were conducted by a sports cardiologist.

Resting ECG

A resting 12-lead ECG was recorded in supine position after 5 mins of rest and analyzed using the Seattle Criteria⁴ by a sports cardiologist.

Resting Transthoracic Echocardiography

The TTE was performed by a sports cardiologist and analyzed according to American Society of Echocardiography recommendations.¹⁷ All measurements were averaged from 3 consecutive cardiac cycles.

Cardiac MRI

A standard cardiac volumes, wall dimension, function, and late gadolinium enhancement (LGE) sequence was performed on a dedicated scanner with full myocardial coverage based on Society for Cardiovascular Magnetic Resonance guidelines. LV and right ventricular (RV) volumes, mass, and function were quantified using customized analysis software by a blinded, single experienced investigator. Wall motion was analyzed based on the 16-segment American Heart Association/American College of Cardiology model. Imaging for LGE to identify fibrosis was performed 5 to 10 minutes after 0.1 mmol/kg gadolinium contrast injection in identical short-axis planes to cine images using a breath-hold inversion-recovery (fast low-angle shot) gradient echo sequence.¹⁸

Maximal Exercise Test

Athletes performed a maximal exercise test with continuous ECG monitoring, either on ergocycle or on treadmill in accordance with their sport specificity. Exercise was stopped because of exhaustion or ominous cardiovascular signs or symptoms. Specific attention was paid to a correction or worsening of PTWI, ST depression (>1 mm), or cardiac arrhythmia. Blood pressure was measured every 2 minutes using a manual sphygmomanometer. Maximal oxygen consumption (VO_2 max) was estimated according to maximal exercise power sustained.¹⁹

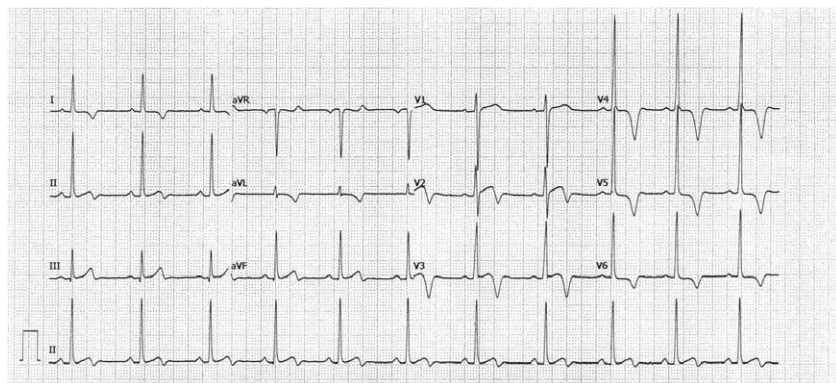


Figure 1. Example of ECG with isolated pathological T wave inversion.

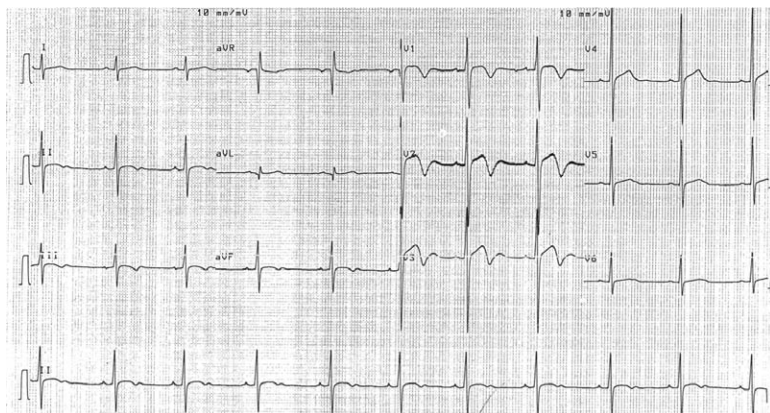


Figure 2. Example of ECG with physiological T wave inversion in V1 through V3 preceded by convex/domed ST segment in an Afro-Caribbean athlete. This ECG pattern was not included in the study in accordance with the Seattle Criteria.⁴

24h ECG Holter

Athletes underwent 24h Holter including a training session for cardiac arrhythmia evaluation. Nonsustained supraventricular and ventricular tachycardias were defined as ≥ 3 consecutive premature beats lasting <30 seconds.

Longitudinal Cardiovascular Follow-Up

Athletes with cardiomyopathies were excluded from competition, but were provided with individualized treatment and appropriate review. Athletes presenting with normal initial evaluations underwent yearly cardiovascular evaluation that included clinical examination, ECG, TTE, maximal exercise test, and Holter. CMR was repeated in those athletes who subsequently presented new cardiovascular data suggestive of pathology on review or when the initial CMR was doubtful. Athletes who became symptomatic during follow-up were automatically requested to undergo cardiac evaluation.

Diagnostic Criteria

For each noninvasive investigation, the investigator was blinded to the result of previous investigation. After complete cardiovascular investigation, athletes were identified as having either (1) a normal heart, (2) a heart suspicious but not diagnostic of cardiac disease, or (3) a cardiac disease diagnosed by 2 sport cardiologists having access to the results of all examinations. A diagnosis of cardiac disease was made in accordance with current guidelines.^{15,20–24}

Because of difficulty distinguishing between the athlete's heart and mild forms of cardiomyopathy, we used established criteria (see Table 1) to define pathology.²² To diagnose HCM, we used the latest European Society of Cardiology (ESC) guidelines to diagnose and manage HCM.²⁴ The criteria include a familial history of HCM in a first-degree relative, unusual patterns of LV hypertrophy (asymmetrical septal hypertrophy, apical hypertrophy), small left ventricular cavity (left ventricular end diastolic diameter <45 mm), systolic anterior motion and left ventricular outflow obstruction, diastolic dysfunction, LGE on CMR, complex ventricular arrhythmias, and an abnormal VO_2 max.^{1,25} Thus, each diagnosis of HCM was validated with the combination of PTWI, abnormal wall thickness (WT) value (see Table 1) and ≥ 1 of the criteria documented above. In all cases, modifications to conclusions drawn on the athlete's first cardiac evaluation were made if during follow-up cardiac disease was expressed; except, however, for the effects of requested detraining on cardiac hypertrophy.

Data Collection and Statistical Analysis

Statistical analysis was performed using SPSS (v.15; Chicago, IL). Most quantitative variables did not follow a normal distribution, thus a Mann–Whitney test was used for comparison of cardiac variables between athletes presenting with/without cardiac disease. Data were expressed as medians with 25th and 75th percentiles or percentage unless otherwise specified. A P value <0.05 was considered statistically significant.

Results

Of 6372 competitive athletes ($n=5726$ male and $n=646$ female) referred for precompetitive sporting evaluation, 155 (2.4%) athletes presented with PTWI median age 27.0 years (range, 20–39) and were included in the study. The prevalence of PTWI from 6372 athletes screened was 2%, 4.8% and 1.9% in white, Afro-Caribbean, and West-Asian male athletes, whereas in females, PTWI was 0.5% and 1.6% in white and Afro-Caribbean athletes. From the 155 athletes with PTWI (149 men; 96.1%), 85 were white (54.8%), 64 were Afro-Caribbean (41.3%), and 6 were West-Asian (3.9%). The athletes trained 10.0 hours/week (range, 6.0–12.0) in either mixed sports (soccer, basketball, handball, or rugby, $n=94$) or endurance sports (running, cycling, or swimming, $n=61$).

Results From Primary Investigations

Medical History and Physical Examination

Familial history was positive in 9 (5.8%) athletes; 5 cases of SCD (3 of unknown origin, 1 HCM, 1 DCM) and 4 cases of cardiomyopathy (3 HCM, 1 ARVC). No athlete presented a personal history of known cardiomyopathy. Systolic cardiac murmurs was observed in 16 (10.3%) athletes.

ECG

Inferior or lateral PTWI were the most commonly observed abnormalities (83.9%; Table 2), followed by precordial lead PTWI (8.4%) and anterior (V1–V4) PTWI (6.5%). PTWI was largely isolated (43.2%), but associated ECG abnormalities such as ST-segment depression (31%), left atrial hypertrophy (29.0%), and abnormal Q waves (11.0%) were commonly observed.

Echocardiography (TTE)

The TTE was normal in 86 (55.5%) athletes, with 37 (23.9%) athletes demonstrating an abnormal TTE; 31 cases of HCM, 3 ARVC, 2 LVNC, and 1 case of significant segmental systolic dysfunction (Figure 3). TTE was suspicious but not diagnostic of a cardiac disease in a further 32 (20.6%) athletes (30 with possible HCM and 2 with possible ARVC).

CMR

The CMR was normal in 69 (44.5%) athletes and abnormal in 61 (39.3%), with 51 cases of HCM, 4 ARVC, 2 LVNC, and 4 myocarditis. CMR was suspicious but not diagnostic of a

Table 1. Criteria Used for Suspicious and Abnormal Conclusions

	Suspicious	Abnormal
Echocardiography		
Hypertrophic cardiomyopathy	13 mm ≤ WT <15 mm and LVEDD ≤55 mm in men 12 mm ≤ WT <15 mm and LVEDD ≤50 mm in women and children	WT ≥15 mm + additional abnormal criteria*
Dilated cardiomyopathy	LVEDD >60 mm (32 mm·m ⁻²) and LVEF <50%	LVEDD >65 mm (33 mm·m ⁻²) and LVEF <45%
Arrhythmogenic RV cardiomyopathy	Unbalanced RV dilation with normal RV wall motion	Unbalanced RV dilation and RV wall motion abnormality
Left ventricular noncompaction		End systolic NC/C >2 and LVEF <50%
Myocarditis†	Isolated wall motion abnormality	
MRI		
Hypertrophic cardiomyopathy	WT ≥13 mm in men or ≥12 in women and children with no appropriate LV dilation	WT ≥15 mm + additional abnormal criteria*
Arrhythmogenic RV cardiomyopathy	RV/LV ≥1.2	RV/LV ≥1.2 and RV wall motion abnormality and / or RV fibrosis
Left ventricular non compaction		Diastolic NC/C >2,3 and LVEF <50%
Dilated cardiomyopathy	LVEDV > 97 mL·m ⁻² and LVEF <50%	LVEDV >120 mL·m ⁻² and LVEF <45%
Myocarditis		Non ischemic LGE
Exercise test	Ventricular couplets	NSVT or SVT VO ₂ max <80% theoretical value
Holter ECG	Ventricular couplets	NSVT or SVT

LGE indicates late gadolinium enhancement; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; NC/C, noncompaction/compaction myocardium; NSVT, nonsustained ventricular tachycardia; RV, right ventricular; SVT, sustained ventricular tachycardia; and WT, wall thickness.

*Additional abnormal criteria: familial history of HCM in a first-degree relative, unusual patterns of LV hypertrophy (asymmetrical septal hypertrophy, apical hypertrophy), small left ventricular cavity (left ventricular end diastolic diameter <45 mm), systolic anterior motion (SAM), and left ventricular outflow obstruction, diastolic dysfunction, LGE on CMR, complex ventricular arrhythmias and an abnormal VO₂ max.

†Myocarditis was proven with CMR

cardiac disease in a further 25 (16.1%) athletes (23 possible HCM and 2 possible ARVC).

Maximal Exercise Test and 24h ECG Holter

Exercise testing was obtained in 141 (91%) athletes, with 89.3% demonstrating a normal investigation. Partial or complete normalization of PTWI during exercise was observed in 79% of athletes. However in 8 (5.7%) cases exercise testing was abnormal, 5 athletes demonstrated nonsustained supra-ventricular tachycardia (3 ARVC, 1 LVNC and 1 myocarditis), 1 athlete demonstrated a drop in blood pressure (LVNC),

Table 2. Main ECG Patterns Observed in Global Population

Parameters	Global Population (n=155)
Heart rate, bpm	59.0 [52.0–65.0]
First-degree AV block	19 (12.3%)
Second-degree Mobitz 1 AV block	1 (0.6%)
Left atrial hypertrophy	45 (29.0%)
Abnormal Q wave	17 (11.0%)
Sokolow index > 35 mm	83 (53.5%)
PTWI localization	
All precordium	13 (8.4%)
V1–V4	10 (6.5%)
Lateral leads	23 (14.8%)
I–aVL	0
V5–V6	16 (10.3%)
I–aVL + V5–V6	7 (4.5%)
II–III–aVF	7 (4.5%)
II–III–aVF + V5–V6	100 (64.5%)
II–III–aVF + V1–V3	1 (0.6%)
I–aVL + V1–V3	1 (0.6%)
ST depression localization	
ST depression	48 (31.0%)
All precordium	2 (1.3%)
V1–V4	1 (0.6%)
V5–V6	16 (10.3%)
I–aVL + V5–V6	4 (2.6%)
II–III–aVF	9 (5.8%)
II–III–aVF + V5–V6	16 (10.3%)

AV indicates atrioventricular; and PTWI, pathological T-wave inversion.

and 2 athletes demonstrated a poor aerobic capacity (2 HCM). Finally, 7 (5%) athletes presented nonspecific ECG abnormalities during exercise; 1 case of junctional tachycardia and 6 cases of ventricular couplets (2 HCM, 1 possible HCM, 1 ARVC, 1 myocarditis, and 1 DCM). Twenty-four-hour ECG Holter was recorded in 109 (70.3%) athletes and was normal in 88% of cases. Nine (8.3%) athletes demonstrated episodes of nonsustained supra-ventricular tachycardia (6 HCM, 1 ARVC, 2 myocarditis).

Longitudinal Follow-Up Results

After primary investigation, 64 athletes with proven cardiac disease were excluded from competitive sport, with 91 athletes identified as having either a normal heart or a heart suspicious but not diagnostic of cardiac disease and were followed up for 12.0 months (range, 8.0–30.0).

Medical History and Physical Examination

During follow-up, 3 (3.3%) athletes developed ominous symptoms; 1 exercise-related aborted cardiac arrest (unknown cause), 1 episode of syncope (unknown cause but with a familial history of sudden death), and 1 symptoms suggestive of heart failure (1 DCM).

ECG, TTE, Exercise Test, and CMR Imaging

CMR was repeated in 27 athletes; 25 for an initial doubtful CMR and 2 who became symptomatic. No athlete

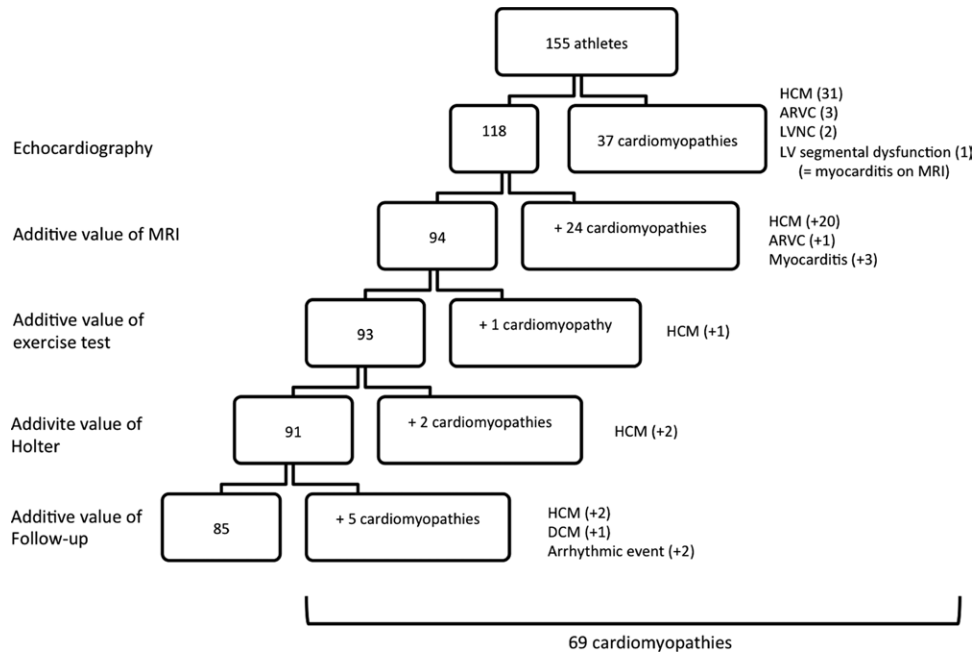


Figure 3. Respective contribution of cardiovascular exams performed. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; and LVNC, left ventricular non compaction.

demonstrated a progressive worsening of PTWI or presented new ECG abnormalities during follow-up. However, systolic dysfunction was observed to have developed in 1 athlete with presenting with clinical symptoms (1 DCM). No abnormal exercise test results were observed in followed athletes. One athlete developed HCM with LGE evident, whereas 1 athlete presenting initially as suspicious but not diagnostic of cardiac disease demonstrated apical HCM.

Overall Identification of Pathology

In conclusion, an identifiable cardiac disease was demonstrated in 44.5% (n=69) of athletes presenting with PTWI. HCM (n=56; 36.1%) was the most commonly identified pathology, followed by ARVC (n=4; 2.6%), myocarditis (n=4; 2.6%), LVNC (n=2; 1.3%), DCM (n=1; 0.6%), and arrhythmic event (n=2; 1.3%; Table 3). Although a diagnosis was identified on initial presentation in the majority of athletes (n=64; 92.8%), a further 5 (7.2%) expressed disease during follow up (Figure 3).

Hypertrophic Cardiomyopathy Diagnosis

A diagnosis of HCM was established in 54 cases (34.8%) during primary investigation. In 44 cases, the WT was ≥ 15 mm with a LV end diastolic diameter ≤ 55 mm. The diagnosis

of HCM was confirmed because of the association with ≥ 1 of the following criteria: family history (n=4), unusual pattern of LV hypertrophy (n=29), LV end diastolic diameter < 45 mm (n=12), systolic anterior motion (n=8), diastolic dysfunction (n=3), LGE with MRI (n=19), complex ventricular arrhythmia (n=3), and an abnormal VO_2 max (n=1). There were 4 cases of patients presenting a WT ≥ 15 mm but with a LV end diastolic diameter > 55 mm. However, a diagnosis of HCM was made because of the presence of LGE (n=3) and typical apical hypertrophy (n=1). Finally, there were 6 cases presenting a maximal wall thickness between 14 and 15 mm; 3 with LGE, 2 with complex ventricular arrhythmias, and 1 with an LV end diastolic diameter < 45 mm and a markedly reduced VO_2 max, ultimately leading to the conclusion that the hypertrophy observed was pathological. All patients with pathological hypertrophy underwent a 3-month period of athletic detraining, with 40 patients undergoing 6 months. In all cases, no significant wall thickness regression was observed.

Efficacy of TTE Versus CMR

From the 69 athletes diagnosed with pathology, TTE was abnormal in 53.6% (n = 37), with CMR confirming 100% of all TTE abnormalities (Figure 3). CMR identified cardiac pathology in a further 24 athletes (34.8%); 10 presenting with a heart suspicious but not diagnostic of cardiac disease and 14 athletes demonstrating normal hearts on TTE. Thus, CMR was able to establish a diagnosis in 88.4% (n=61) of athletes.

Clinical Value of the Maximal Exercise Testing and 24h ECG Holter

Maximal exercise testing aided in the diagnosis of cardiac pathology in 8 (5.7%) athletes, of which 7 had ≥ 1 abnormal imaging result and 1 who presented a suspicious imaging result. Twenty-four-hour ECG Holter was abnormal in 9

Table 3. Overall Cardiac Diseases Identified (n=69)

Cardiac disease	Number of Patients
Hypertrophic cardiomyopathy	56
Dilated cardiomyopathy	1
Arrhythmogenic right ventricular cardiomyopathy	4
Left ventricular noncompaction	2
Myocarditis	4
Arrhythmic events without morphological cardiomyopathy	2

athletes, but was associated with abnormal imaging in 7 and in 2 athletes with imaging suspicious but not diagnostic of cardiac disease (Figure 3).

Predictive Factors of Cardiac Disease in Athletes With PTWI

A familial history of SCD or cardiomyopathy in a first-degree relative and ST-segment depression alongside PTWI were both more frequent in athletes with identified cardiac disease (Table 4). The normalization of PTWI during exercise was more frequent in athletes without cardiac disease, with the localization of PTWI and ethnicity having no impact on the cardiac disease prevalence.

Discussion

This study aimed to prospectively determine the prevalence of cardiac pathology in athletes presenting with PTWI, and to examine the efficacy of including CMR in the battery of further examinations. Our data demonstrate that from 155 athletes presenting with PTWI, 44.5% demonstrate a serious cardiac pathology associated with sudden cardiac death (primarily HCM). CMR significantly increases the diagnostic capability of disease identification, especially in those athletes presenting with a normal echocardiogram. Finally, our data

demonstrate that all athletes presenting with PTWI must be followed up annually before medical clearance for competitive sport can be given, because 5 athletes (7.2% of all positive cases) expressed disease after initially presenting with normal examination.

Prevalence of Cardiac Disease in Athletes Presenting With PTWI

The prevalence of PTWI observed in this study is similar to previously reported figures.^{16,26} It has been clearly demonstrated that in whites, PTWI prevalence (2% to 3%) is no different between athletes and nonathletes,²⁷ but in Afro-Caribbean individuals, the prevalence of PTWI is higher in athletes than nonathletes.¹⁶

Our results reaffirm that marked PTWI is associated with a high prevalence of cardiac pathologies that are associated with conditions that may predispose athletes to SCD.⁹ Although our prevalence of disease is slightly higher than previously reported (45% versus 36%),⁹ in keeping with the majority of studies, HCM was our most common identified pathology (81% of all cases). Accordingly, all athletes with disease were excluded from competitive sports as recommended.¹³

Importance of Annual Cardiovascular Follow-Up

The present study did not observe PTWI normalization during follow-up as previously reported.⁹ Our data demonstrate the importance of annual follow-up, because almost 6% athletes who presented with PTWI but normal secondary investigations in initial examination later went onto develop clear pathology during follow-up.

However, in line with previous recommendations,^{9,14} it is unreasonable to disqualify 55% of athletes presenting PTWI but demonstrating normal secondary investigations. In the case of an asymptomatic athlete with PTWI but normal detailed cardiac evaluation and no family history of hereditary cardiac disease, we recommend unrestricted participation in competitive sports. Accordingly, we would inform and educate the athlete regarding the development of symptoms, and place under yearly cardiac evaluation. Further, we propose a systematic cardiac examination with 12-lead ECG and echocardiography of first-degree relatives (>10 years of age).

Efficacy of Using CMR in Athletes With PTWI

Although the prevalence of an abnormal TTE (24%) was similar to previously published data for athletes presenting with PTWI,⁹ initial TTE missed 46% of all diagnosed pathological cases. CMR provided a diagnosis in 88% of all cardiomyopathies and, importantly, established disease in 30% suspicious TTE and corrected 16.5% of TTE initially considered normal.

Previously, in conjunction with an ECG, echocardiography was considered the standard noninvasive diagnostic test for HCM. The diffuse nature of the disease pattern in HCM, however, limits the usefulness of echocardiography, which often fails to adequately visualize the anterolateral free wall and apex. The distribution of hypertrophy in HCM is often asymmetrical; consequently, subtle segmental areas of hypertrophy may be missed on echocardiography. In particular CMR is vital for assessment of apical hypertrophy and assessment

Table 4. Comparison of Athletes With and Without Cardiac Disease

Parameters	Cardiac Disease (n=69)	No Evidence of Cardiac Disease (n=86)	P
Age, y	30.0 [21.0–41.0]	26.0 [20.0–36.0]	0.09
Males	66 (95.6%)	83 (96.5%)	0.78
White	41 (59.4%)	44 (51.1%)	0.52
Afro-Caribbean	26 (37.7%)	38 (44.2%)	
West-Asian	2 (2.9%)	4 (4.7%)	
Training level (h/week)	8.5 [5.0–12.0]	12.0 [8.0–12.0]	0.07
Familial history	7 (10.1%)	2 (2.3%)	0.04
Systolic murmur	7 (10.1%)	9 (10.5%)	0.95
Left atrial hypertrophy	23 (33.3%)	22 (25.6%)	0.44
Abnormal Q wave	11 (15.9%)	6 (7.0%)	0.07
ST depression	32 (46.4%)	16 (18.6%)	0.0002
Sokolow index, mm	35.0 [28.0–42.0]	39.0 [30.0–45.0]	0.11
Exercise (n=141)	39/56 (69.6%)	59/68 (86.7%)	0.013
PTWI normalization			
PTWI localization			
All precordium	7 (10.1%)	6 (7%)	0.31
V1–V4	3 (4.3%)	7 (8.1%)	0.48
Lateral Leads	9 (13%)	14 (16.3%)	0.34
V5–V6	5 (7.2%)	11 (12.8%)	0.26
I–AVL + V5–V6	4 (5.8%)	3 (3.5%)	0.49
II–III–AVF	3 (4.3%)	4 (4.7%)	0.93
II–III–AVF + V5–V6	47 (68.1%)	53 (61.6%)	0.40
II–III–aVF + V1–V3	0	1 (1.2%)	0.26
I–aVL + V1–V3	0	1 (1.2%)	0.26

PTWI indicates pathological T-wave inversion.

of the anterolateral free wall.^{23,28} Thus, CMR is the reference standard imaging modality for the assessment of ventricular volumes, function, mass, and tissue characterization (eg, myocardial fibrosis) and in our opinion must be included in the work-up at athletes presenting with marked PTWI with normal echocardiographic examinations.

Clinical Value of the Other Examination Modalities

Positive family history rates were significantly higher in athletes diagnosed with a cardiac disease ($P=0.04$) than athletes presenting a normal hearts, demonstrating the importance of ascertaining such details. Sixteen athletes presented a systolic murmur on physical examination, from which 7 were diagnosed with HCM. Exercise testing and 24hr ECG Holter were abnormal in 12% and 18% of athletes, respectively with proven cardiac disease. Importantly, PTWI normalization during exercise was observed in 79% of the population studied, 87% and 70% of the athletes, respectively without and with cardiac disease. Thus, PTWI normalization during exercise cannot be used as a criterion of benignity.

Algorithm for Evaluating Athletes With PTWI

An algorithm for evaluating athletes presenting with PTWI is presented in Figure 4. These propositions are based on findings from the current study and from proven data from the literature.^{1,14}

The Cost of Identifying Pathology

The cost-effectiveness of the entire ECG screening program is not within the scope of this study. However, because of the current debate concerning the cost-effectiveness of ECG screening in athletes,²⁹ we calculated the cost-effectiveness using France medical reimbursement costs for the 155 athlete presenting with PTWI. It cost \$1839 USD per athlete to identify cardiac disease, and \$2620 USD per athlete when annual follow-up costs are included.

Study Limitations

We acknowledge the absence of a gold standard test to diagnose HCM in athletes.²⁴ Despite this, however, we used the latest ESC criteria for diagnosing and managing individuals with HCM. Although the presence of LGE is an important diagnostic feature supporting pathology, its absence does not exclude pathology. Nevertheless, our data support CMR as part of the routine work-up in athletes presenting with PTWI. Genetic testing was not provided for financial reasons. However, in an athlete with an overt cardiomyopathy, the yield of mutation identification is variable according to the disease: 50% to 70% in HCM and $\approx 40\%$ in ARVC. Failure to identify a recognized mutation does not exclude the diagnosis of a cardiomyopathy or ion channelopathy for 3 important reasons: (1) not all genetic regions are assessed, (2) current technology is not able to detect some forms of mutation (intronic cryptic splice sites, large genomic rearrangements, etc), and (3) a similar phenotype may possibly develop without a specific genetic constitution. Finally, complementary CV screening of first-degree relatives was not possible in the majority of athletes because of the international nature of origin, feasibly explaining the lower than expected family history incidence of HCM.

Conclusion

In conclusion, PTWI was associated with cardiac pathology in 45% of athletes, with HCM the most common cardiac disease identified. Furthermore, CMR is paramount to increase the diagnostic capability to identify pathology even in the presence of a normal echocardiogram. Although automatic disqualification is unwarranted, all athletes presenting with PTWI must be followed up annually before medical clearance for competitive sport can be provided.

Acknowledgments

We thank N. Endjah, J.L. Foulgoc, and S. Caudmont for their help in data collection.

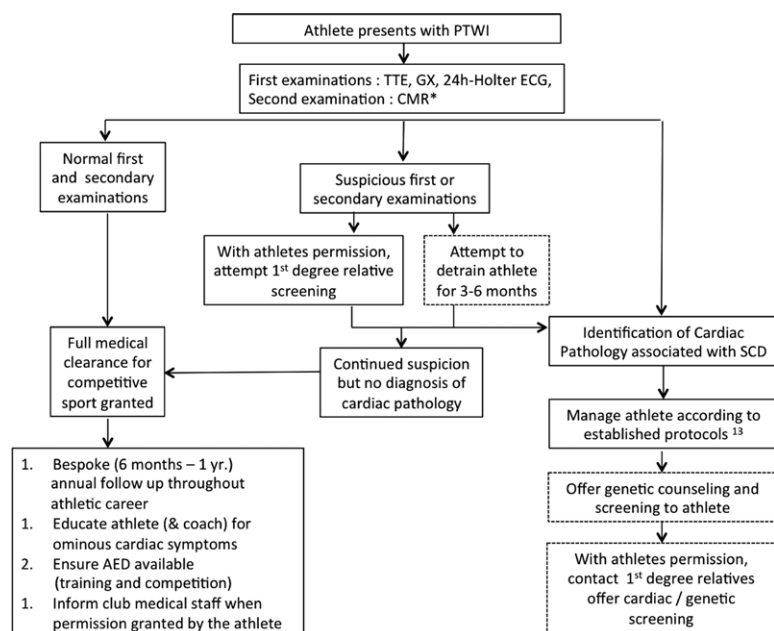


Figure 4. Algorithm for evaluation of athlete presents with TWI. *Note that cardiac magnetic resonance (CMR) is always requested when echocardiography is normal. Dotted lines mean that the evaluation can be proposed to athlete. 24h-Holter ECG indicates 24-hour Holter ECG recording including intensive training session; AED, automatic external defibrillator; GX, maximal exercise test; PTWI, pathological T-wave inversion; SCD, sudden cardiac death; and TTE, resting transthoracic echocardiography.

Sources of Funding

This study has been partly supported with a grant from “Bourse Fabrice Salanson” from Club des Cardiologues du Sport.

Disclosures

None.

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CLINICAL PERSPECTIVE

Although rare, the observation of pathological T-wave inversion (PTWI) on the resting 12-Lead ECG of an asymptomatic athlete is one of the most serious sports cardiology issues. Indeed, PTWI is observed in several cardiac diseases related to sudden death in athletes. In the absence of documented pathology on secondary investigation, competitive sport may be authorized. Consequently, the true nature of PTWI in an asymptomatic athlete is not yet clearly defined or understood. This prospective study examined a large group of asymptomatic athletes (n=155), all presenting with PTWI. Athletes were well phenotyped with echocardiography and cardiac magnetic resonance (CMR), and were routinely followed up for a number of years. A diagnosis of cardiac disease was established in 45% of athletes, with hypertrophic cardiomyopathy (81%) the most common pathology. Once considered the gold standard secondary investigation, echocardiography missed a diagnosis of pathology in 35% of PTWI athletes, who were subsequently identified with disease on CMR imaging. This result supports CMR's mandatory inclusion in the workup of athletes presenting with PTWI in case of normal echocardiography. Finally, this study also establishes the clear role for annual cardiovascular follow-up, because 7% of athletes initially granted authorization to play competitive sports later went on to develop cardiac pathology in subsequent years.

Recognition and Significance of Pathological T-Wave Inversions in Athletes

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Circulation. 2015;131:165-173; originally published online November 10, 2014;
doi: 10.1161/CIRCULATIONAHA.114.011038

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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2. Athlètes avec CMH: un phénotype particulier

Dans l'étude précédente, nous avons constaté que les critères diagnostique de CMH établis par les dernières recommandations européennes n'étaient pas toujours faciles à appliquer et faisaient débat ^{57,58}. Nous avons par exemple constaté que peu d'athlètes avec CMH présentaient une dysfonction diastolique (3 sur les 56 CMH). Par ailleurs, certains athlètes porteurs d'une CMH étaient capables de réaliser des performances sportives de haut niveau sans symptôme. Il est donc probable que ces athlètes avec CMH ont des caractéristiques phénotypiques différentes que les CMH sédentaires.

Jusqu'alors, toutes les données de la littérature sur la différenciation entre cœur d'athlète et CMH n'avaient inclus que des sujets sains sportifs versus des CMH sédentaires ^{29,59}. Aucune étude n'avait inclus de cohorte de sujets sportifs avec une CMH authentifiée. Dans cette étude collaborative nous avons souhaité lever ce biais de sélection en participant à une étude multicentrique permettant de mieux caractériser le phénotype réel des athlètes avec CMH.

Compte tenu du faible nombre d'athlètes porteurs d'une CMH, il est de nouveau apparu indispensable de mettre en commun nos données.

Apport du candidat dans ce travail

40% des CMH sportif de ce travail sont issus de la base de données des CMH rennaise.
Relecture et correction du manuscrit.

RESUME

Objectifs: Le phénotype des individus atteints de cardiomyopathie hypertrophique (CMH) et qui pratiquent une activité physique régulière est méconnu. L'objectif de cette étude était de mieux caractériser le profil clinique de jeunes athlètes avec CMH.

Méthodes et résultats : Les paramètres électriques, structurels, et fonctionnels cardiaques de 106 jeunes (14-35 ans) athlètes avec CMH ont été comparés avec ceux de 101 CMH sédentaires. Un sous-groupe d'athlètes ayant une CMH concentrique modérée (13-16mm) a été comparé avec 55 athlètes sains ayant une hypertrophie ventriculaire gauche (HVG) physiologique. La plupart des athlètes avec CMH (96%) présentaient des ondes T négatives et avaient une HVG moindre ($15.8 \pm 3.4\text{mm}$ vs. $19.7 \pm 6.5\text{mm}$, $P < 0.001$), des cavités VG plus larges ($47.8 \pm 6.0\text{mm}$ vs. $44.3 \pm 7.7\text{mm}$, $P < 0.001$) et une meilleure fonction diastolique ($E/e' 7.9 \pm 2.4$ vs. 10.7 ± 3.9 , $P < 0.001$) que les CMH sédentaires. Chez les athlètes avec CMH, l'HVG était fréquemment (36%) limitée à l'apex, seulement 15 individus (14%) présentaient une HVG concentrique modérée mimant une HVG physiologique. Chez ces 15 athlètes, les paramètres cardiaques structurels conventionnels et fonctionnels montraient une sensibilité et une spécificité modestes pour différencier CMH et HVG : 13% avaient une cavité VG $> 54\text{mm}$, 87% avaient une oreillette gauche $\leq 40\text{mm}$ et 100% un rapport $E/e' < 12$.

Conclusions : Les athlètes avec une CMH ont une HVG moindre, des cavités VG plus larges, et des indices de fonction diastolique normaux en comparaison avec les CMH sédentaires. Seule une minorité des athlètes avec CMH est dans la zone grise conventionnelle d'HVG concentrique modérée. Dans cette minorité, les paramètres échocardiographiques conventionnels sont insuffisants pour différencier CMH et HVG physiologique. Ils doivent être complétés par l'analyse d'autres paramètres afin de minimiser le risque de faux négatifs

Clinical Profile of Athletes With Hypertrophic Cardiomyopathy

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Vasileios Panoulas, MD, PhD; Aneil Malhotra, MRCP; Mathew Wilson, PhD;
François Carré, PhD; Sanjay Sharma, MD

Background—The phenotype of individuals with hypertrophic cardiomyopathy (HCM) who exercise regularly is unknown. This study characterized the clinical profile of young athletes with HCM.

Methods and Results—The electrical, structural, and functional cardiac parameters from 106 young (14–35 years) athletes with HCM were compared with 101 sedentary HCM patients. A subset of athletes with HCM exhibiting morphologically mild (13–16 mm), concentric disease was compared with 55 healthy athletes with mild physiological left ventricular hypertrophy (LVH). Most athletes with HCM (96%) exhibited T-wave inversion and had milder LVH (15.8±3.4 mm versus 19.7±6.5 mm, $P<0.001$), larger left ventricular cavity dimensions (47.8±6.0 mm versus 44.3±7.7 mm, $P<0.001$), and superior indices of diastolic function (average E/E' 7.9±2.4 versus 10.7±3.9, $P<0.001$) compared with sedentary HCM patients. In athletes with HCM, LVH was frequently (36%) confined to the apex and only 15 individuals (14%) exhibited mild concentric LVH mimicking physiological LVH. In these 15 athletes, conventional structural and functional cardiac parameters showed modest sensitivity and specificity for differentiating HCM from physiological LVH: 13% had a left ventricular cavity >54 mm, 87% had a left atrium ≤40, and 100% had an $E/E' <12$.

Conclusions—Athletes with HCM exhibit less LVH, larger left ventricular cavities, and normal indices of diastolic function compared with sedentary patients. Only a minority of athletes with HCM constitute the conventional gray zone of mild, concentric LVH. In this minority, conventional echocardiographic parameters alone are insufficient to differentiate HCM from physiological LVH and should be complemented by additional structural and functional assessments to minimize the risk of false reassurance. (*Circ Cardiovasc Imaging*. 2015;8:e003454. DOI: 10.1161/CIRCIMAGING.114.003454.)

Key Words: echocardiography ■ exercise physiology ■ hypertrophic cardiomyopathy ■ left ventricular hypertrophy ■ primary prevention

Hypertrophic cardiomyopathy (HCM) is a heterogeneous condition with highly variable phenotypic expression and is the leading cause of sudden cardiac death in young athletes worldwide.¹ The clinical profile of athletes with HCM capable of competing in sporting activities at an extraordinarily high level has not been characterized. Traditional methods for differentiating physiological left ventricular hypertrophy (athlete's heart) from HCM have relied on parameters derived from sedentary HCM patients and healthy athletes.^{2–5} Anecdotal evidence suggests that such algorithms² may not be directly applicable to athletes with HCM.^{6–8}

The results were compared with young sedentary HCM patients to determine differences in disease phenotype between individuals with HCM who exercise regularly and those who are sedentary. The results from a small subset of athletes with HCM revealing mild (13–16 mm) concentric left ventricular hypertrophy (LVH) were also compared with a group of healthy athletes with physiological LVH to ascertain the reliability of current discriminating structural and functional left ventricular (LV) parameters used to differentiate between the 2 entities.

Methods

Setting

This study was collaboration between 2 specialist cardiomyopathy centers in the United Kingdom and France. These institutions receive direct referrals from preparticipation cardiovascular evaluation of young professional athletes, including those suspected with HCM.

See Clinical Perspective

This study sought to characterize the clinical profile of young athletes with HCM diagnosed during preparticipation cardiovascular evaluation or in the context of family

Received December 17, 2014; accepted June 15, 2015.

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Circ Cardiovasc Imaging is available at <http://circimaging.ahajournals.org>

DOI: 10.1161/CIRCIMAGING.114.003454

St George's Hospital (London, United Kingdom) and the French Institute of Health and Medical Research (Rennes, France) are dedicated Sports Cardiology centers and work closely with the charitable organization Cardiac Risk in the Young and the French National Sports Ministry, respectively, both of whom conduct National screening programs for elite athletes. Since 2010, both institutions have received referrals from Qatar Orthopedic and Sports Medicine Hospital (Doha, Qatar), which has a highly active cardiovascular screening program that serves the entire Persian Gulf region. All elite athletes receive a 12-lead ECG and 2-dimensional echocardiography as part of these screening programs.⁹

Athletes With HCM

Between 2000 and 2014, 106 consecutive, young (aged 14–35 years), asymptomatic athletes were diagnosed with HCM. The preliminary cardiac investigations resulting in the diagnosis were conducted during a period when these athletes were still actively engaged in competitive sports and before any decision regarding disqualification or cessation of exercise. Of the 106 athletes, 78 (76%) were detected during sports participation screening, and the remainder were identified through familial screening. All athletes with HCM competed at regional, national, or international level and 86 (81.1%) had performed at national or international level during their career. Athletes with HCM competed in a range of sports, including soccer (n=41, 38.7%), rugby (n=11, 10.4%), basketball (n=11, 10.4%), tennis (n=7, 6.6%), cycling (n=4, 3.8%), handball (n=4, 3.8%), distance running (n=4, 3.8%), swimming (n=3, 2.8%), and a mix of other sports (n≤2/sport; n=21, 19.8%). All individuals had baseline blood pressures of <140/90 mm Hg.

The diagnosis of HCM was based on LVH >16 mm in any myocardial segment, as assessed on echocardiography and cardiac MRI (CMRI), in the absence of another cardiac disorder or systemic condition capable of producing the same magnitude of LVH.^{10,11} In cases of mild LVH, HCM was diagnosed in the context of a combination of features, including (1) identification of HCM in a first-degree relative; (2) nonconcentric patterns of LVH; (3) dynamic left ventricular outflow tract obstruction; (4) late gadolinium enhancement (LGE) on CMRI; or (5) an established pathogenic gene mutation.^{2,12} Importantly, the combination of electrocardiographic anomalies and mild concentric LVH were not considered diagnostic of HCM in the absence of additional features.

Sedentary HCM Patients

To establish potential phenotypic differences between individuals with HCM who engage in competitive sport, and those who are sedentary, electrocardiographic, echocardiographic, and CMRI data from athletes with HCM was compared with 101 consecutive sedentary HCM patients of similar age, sex, and ethnicity selected from a database of 550 patients at St George's Hospital.

Healthy Athletes With Mild LVH

A second comparison was made between 15 of the 106 athletes with HCM who expressed mild concentric LVH (13–16 mm) and 55 healthy athletes with mild physiological LVH (13–16 mm). The latter were selected from a database of 3210 elite athletes evaluated between 2000 and 2012 with ECG and transthoracic echocardiography, as previously reported.⁹ These athletes competed in a range of sports, including soccer (n=12, 21.8%), rugby (n=8, 14.5%), rowing (n=6, 10.9%), boxing (n=5, 9.1%), cycling (n=4, 7.3%), swimming (n=3, 5.5%), and a mix of other sports (n≤2/sport; n=17, 31%). All healthy athletes underwent cardiopulmonary exercise testing, 24-hour Holter monitoring, and CMRI as part of additional work-up to exclude HCM. Figure 1 summarizes the 2 comparison arms.

Investigations in Athletes and Sedentary HCM Patients

All individuals with HCM (both athletes and sedentary patients) and healthy athletes with physiological LVH were evaluated as follows.

For the purposes of this study, electrocardiographic and echocardiographic analysis was performed on the presenting ECG and echocardiogram.

Electrocardiography

Electrocardiography was performed using standard 12-lead positions using a GE Marquette Hellige (Milwaukee, USA) or Philips Pagewriter Trim III (Bothel, Washington) as described elsewhere.⁹ Electrocardiograms were analyzed and deemed normal or abnormal in accordance with current European recommendations.¹³ T-wave inversion of ≥ -0.1 mV in ≥ 2 leads was considered significant (excluding AVR, V1+lead III in isolation). Biphasic T-wave inversion was counted as abnormal if the negative deflection of the T-wave exceeded ≥ -0.1 mV. Deep T-wave inversion was defined as a T-wave deflection ≥ -0.2 mV.

Echocardiography

Two-dimensional echocardiography was performed using either a GE Vivid I (Tirat, Israel), Philips Sonos 7500, Philips iE33, or Philips CPX50 (Bothel, Washington). Standard views were obtained and cavity and wall thickness measurements performed using established guidelines.¹⁴ LV wall thickness was measured in the parasternal long axis at end-diastole and the parasternal short axis at end-diastole at the levels of the mitral valve, papillary muscles, and apex, with the maximal LV wall thickness defined as the greatest measurement obtained. The relative wall thickness was derived by dividing the sum of the end diastolic LV septal and posterior wall thicknesses by the left ventricular end diastolic dimension (LVEDD). Pulsed Doppler recordings were performed at the distal margins of the mitral valve leaflets for early (E) and late (A) diastolic velocities. Tissue Doppler imaging of septal and lateral mitral annular movement was recorded from the apical 4-chamber views to obtain systolic (S') and diastolic early (E') and late (A') peak velocities.¹⁵ The ratio of the E velocity to the E' septal and lateral annular velocities were averaged to provide an index of diastolic function.¹⁶ Left ventricular ejection fraction was calculated from LV volumes using Simpson's rule.¹⁴

Further Investigations

Further investigations in all individuals with HCM included a maximal exercise tolerance test, 24-hour Holter monitor, and CMRI.¹⁷ Additionally, athletes with HCM were subject to an upright cardiopulmonary exercise test using a COSMED E100w cycle ergometer (Rome, Italy).¹⁸

Ethical and Institutional Review Board Approval

Ethical approval was granted by the National Research Ethics Service, Essex 2 Research Ethics Committee in the United Kingdom, the French Ministry of health and youth in France, and Shafallah Medical Genetic Center in Qatar. The study was approved by an institutional review committee, and all participants gave informed consent.

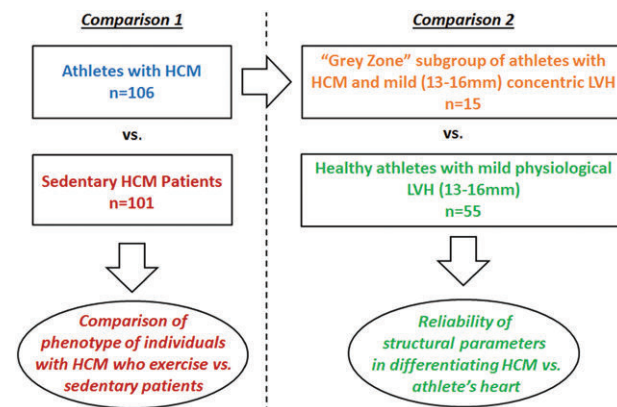


Figure 1. Comparison arms of the study. HCM indicates hypertrophic cardiomyopathy; and LVH, left ventricular hypertrophy.

Table 1. Demographics of Athletes With HCM and Sedentary HCM Patients

Parameter	Athletes With HCM, n=106	Sedentary HCM Patients, n=101	P Value
Age at presentation, y	24.3±6.9	25.8±6.0	0.101
Male sex, %	94.3	90.1	0.253
Ethnicity, %			0.763
White	59.4	64.4	
Black	33.3	28.7	
Asian	7.5	6.9	
Body surface area, m ²	1.95±0.18	2.00±0.27	0.299
Systolic blood pressure, mm Hg	122.7±11.9	121.27±14.8	0.443
Diastolic blood pressure, mm Hg	72.7±10.7	74.1±10.7	0.537
Family history of HCM or SCD, %	26.4	47.5	0.002
Murmur on examination, %	16.5	33.7	0.005

HCM indicates hypertrophic cardiomyopathy; and SCD, sudden cardiac death.

Statistical Analysis

Data were expressed as mean±standard deviation or percentages as appropriate and analyzed using IBM SPSS software, version 20 (Armonk, NY). Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Group differences were tested using Student's *t* test or Mann–Whitney U test for normally and non-normally distributed variables, respectively. The chi-squared test or Fisher exact test was used as appropriate to test group differences of proportions. To identify the most parsimonious predictors of athletic status in HCM patients, stepwise logistic regression (forward likelihood ratio) was used. Variables included in the model consisted of those identified as significant predictors of athletic status in univariate analysis and those considered clinically important. Receiver operating characteristic curve analysis was used to test the sensitivity and specificity of those variables that showed significant differences between athletes with morphologically mild concentric HCM and healthy athletes with physiological LVH. Optimal cut-off values, defined as the best compromise between sensitivity and specificity, were calculated by Youden's Index. Significance was defined as a 2-tailed *P* value of <0.05 throughout.

Results

Comparison of Athletes With HCM to Sedentary HCM Patients

Demographics

There were no significant differences between athletes with HCM and sedentary HCM patients with respect to age, sex, ethnicity, body surface area, and blood pressure profile (Table 1). A higher proportion of sedentary patients had a family history of HCM, a family history of sudden cardiac death, or a cardiac murmur.

Electrocardiographic Changes

The electrocardiographic differences between athletes with HCM and sedentary HCM patients are illustrated in Table 2. T-wave inversion was common in all individuals with HCM, but was more frequent in the athletic cohort compared with sedentary patients (96.2% versus 84.2%, *P*=0.003). The majority of T-wave inversion in both groups was deep and affected the lateral leads. There were no significant differences

between the groups with respect to other abnormal ECG patterns.¹³ Two athletes with HCM had an entirely normal ECG. The diagnosis of HCM in these individuals was triggered by an abnormal echocardiogram and a positive family history for the condition.

Structural Changes

The echocardiographic and CMRI characteristics of athletes with HCM and sedentary HCM patients are presented in Table 3. Athletes with HCM exhibited a lower mean maximal left ventricular wall thickness compared with sedentary patients (15.8±3.4 versus 19.7±6.5 mm, *P*<0.001) and a larger LVEDD (47.8±6.0 versus 44.3±7.7 mm, *P*<0.001). Correspondingly, the relative wall thickness was smaller in athletes with HCM compared with sedentary patients (0.57±0.21 versus 0.71±0.34, *P*<0.001). In total, 15 (14.2%) athletes with HCM revealed an LVEDD of >54 mm. Important differences were observed in the pattern of LVH between athletes with HCM and sedentary patients. Asymmetrical septal hypertrophy was the predominant pattern in both groups, but athletes with HCM were more likely to exhibit apical LVH (35.8% versus 11.9%, *P*<0.001; Figure 2). Of note, only 15 (14.2%) athletes with HCM exhibited concentric LVH.

The LV end-diastolic volumes measured on CMRI were greater in athletes with HCM compared with sedentary HCM patients. There were, however, no differences in LV mass between the 2 groups. A similar proportion of athletes with HCM and sedentary patients revealed LGE.

Table 2. Electrocardiographic Characteristics of Athletes With HCM and Sedentary HCM Patients

Electrocardiographic Parameter	Athletes With HCM, n=106	Sedentary HCM Patients, n=101	P Value
Heart rate, bpm	59.9±9.9	67.1±14.3	<0.001
Sinus rhythm, %	100	98.0	0.145
1st degree heart block, %	11.5	8.6	0.496
Left-axis deviation, %	7.5	11.9	0.291
Right-axis deviation, %	1.9	5.9	0.130
Left bundle branch block, %	0.0	5.0	0.020
Right bundle branch block, %	1.9	4.0	0.374
Right ventricular hypertrophy*, %	11.5	18.9	0.145
Left ventricular hypertrophy*, %	61.3	51.5	0.154
Left atrial enlargement, %	39.6	37.6	0.768
Right atrial enlargement, %	17.9	17.8	0.985
Pathological Q-waves, %	23.6	19.8	0.510
TWI, %	96.2	84.2	0.003
Confined to V1–V4	0.9	4.0	0.158
Extending to inferior leads	9.4	6.9	0.512
Extending to lateral leads	85.8	73.3	0.024
Deep TWI, %	85.7	73.3	0.027
ST-segment elevation, %	63.8	49.5	0.038
ST-segment depression, %	57.1	42.6	0.049
QRS fragmentation, %	22.3	39.6	0.008

HCM indicates hypertrophic cardiomyopathy; and TWI, T-wave inversion.

*By Sokolow–Lyon criteria.

Table 3. Structural Characteristics of Athletes With HCM and Sedentary HCM Patients on Echocardiography and Cardiac MRI

Structural Characteristic	Athletes With HCM, n=106	Sedentary HCM Patients, n=101	P Value
Echocardiography			
Left atrial dimension, mm	38.1±6.5	38.7±8.6	0.347
Left ventricular end diastolic dimension, mm	47.8±6.0	44.3±7.7	<0.001
Maximal left ventricular wall thickness, mm	15.8±3.4	19.7±6.5	<0.001
Relative wall thickness	0.57±0.21	0.71±0.34	<0.001
Fractional shortening, %	41.1±9.3	40.5±10.0	0.391
LVEF, %	67.7±6.6	58.6±12.2	<0.001
Systolic anterior motion of the mitral valve leaflets at rest, %	8.1	23.8	0.002
Resting left ventricular outflow tract gradient ≥30 mmHg, %	2.0	12.0	0.006
Mitral inflow E-wave, m/s	0.79±0.19	0.75±0.17	0.173
Mitral inflow A-wave, m/s	0.49±0.17	0.52±0.16	0.061
Mitral E/A ratio	1.73±0.53	1.55±0.51	0.018
Mitral valve deceleration time	193.9±49.0	193.6±55.7	0.974
Lateral S', m/s	0.10±0.02	0.08±0.02	<0.001
Lateral E', m/s	0.13±0.04	0.10±0.04	<0.001
Lateral E/E'	6.7±2.4	8.9±3.9	<0.001
Septal E', m/s	0.09±0.03	0.07±0.02	<0.001
Septal E/E'	9.3±3.2	12.6±5.3	<0.001
Average E/E'	7.9±2.4	10.7±3.9	<0.001
Mitral regurgitation >mild, %	2.9	30.7	<0.001
Ventricular hypertrophy pattern, %			<0.001
Septal	45.3	50.5	
Apical	35.8	11.9	
Concentric	14.2	2.0	
Mixed	4.7	35.6	
Cardiac MRI, %	66.0	66.3	
Left ventricular end diastolic volume index, mL/m ²	83.6±16.8	73.4±19.5	0.021
LVEF, %	70.8±7.9	72.5±8.9	0.221
Left ventricular mass index, g/m ²	102.6±31.1	104.4±42.3	0.931
Late gadolinium enhancement, %	33.0	40.6	0.258

HCM indicates hypertrophic cardiomyopathy; and LVEF, left ventricular ejection fraction.

Functional Changes

Athletes with HCM showed superior LV diastolic indices compared with sedentary HCM patients, as assessed by Tissue Doppler imaging in both the septal and lateral mitral annulus (Table 3). The average E/E' ratio was smaller in athletes with HCM compared with sedentary HCM patients (7.9±2.4 versus 10.7±3.9, $P<0.001$). The majority of athletes with HCM exhibited diastolic indices within traditionally accepted normal limits;^{19,20} 92.5% had an average E/E' <12,²¹ 59.4% had a septal $E' \geq 0.09$ m/s, and 86.8% had a lateral $E' \geq 0.09$ m/s.

Athletes with HCM demonstrated a lower prevalence of systolic anterior motion of the mitral valve leaflets (SAM), left ventricular outflow tract pressure gradients of ≥ 30 mmHg under basal conditions, and moderate or severe mitral regurgitation compared with sedentary patients.

Exercise Testing and Holter Monitoring

Athletes with HCM obtained mean peak oxygen consumption (pVO_2) of 110%±24% of that predicted for age and sex and a quarter (25.5%) achieved a pVO_2 of $\geq 120\%$ of predicted. Fourteen (13.2%) athletes with HCM displayed abnormalities on exercise testing. Nine athletes with HCM (8.5%) demonstrated a blunted blood pressure response to exercise (systolic rise of <25 mmHg) compared with 23 sedentary HCM patients (22.8%, $P=0.004$). Exercise-induced arrhythmias were observed in 6 (5.6%) athletes with HCM, specifically nonsustained ventricular tachycardia (n=1); supraventricular tachycardia (n=2); atrial fibrillation (n=1); and frequent ventricular ectopics (n=2).

During ambulatory 24-hour Holter monitoring, 13 athletes with HCM (12.3%) revealed arrhythmias, specifically nonsustained ventricular tachycardia (n=9); supraventricular

tachycardia (n=2); and atrial fibrillation (n=2). A further 10 athletes with HCM (9.4%) demonstrated nonspecific findings, namely couplets and triplets (n=7), frequent (>2000/per 24 hours) ventricular ectopic beats (n=2), and a junctional rhythm (n=1).

Multivariable Analysis

Stepwise logistic regression revealed the following variables to be the strongest predictors of athletic status (Table 4): (1) apical or concentric patterns of LVH as opposed to a mixed patterns; (2) lower maximum LV wall thickness; (3) absence of >mild mitral regurgitation; (4) ST-segment elevation on the ECG; (5) absence of QRS fragmentation on the ECG. The final model had a Nagelkerke R^2 of 0.524.

Comparison of Athletes With Morphologically Mild HCM to Healthy Athletes With Physiological LVH

The majority of athletes with HCM exhibited either a left ventricular wall thickness >16 mm (n=48; 45.3%) and non-concentric patterns of LVH (n=91; 85.8%), which would be considered diagnostic of HCM based on current algorithms.²⁻⁵

Fifty-eight athletes with HCM revealed morphologically mild LVH (13–16 mm). Of these, only a small minority exhibited concentric LVH (n=15; 14.2%) consistent with the conventional gray zone.²⁻⁵ These athletes had a higher prevalence of T-wave inversion compared with athletes with physiological LVH (100% versus 5.5%, $P<0.001$). Deep T-wave inversion in the lateral leads (93.3%), pathological Q-waves (26.7%), and ST-segment depression (46.7%) were observed exclusively in athletes with HCM.

Athletes with mild concentric HCM revealed smaller LV cavities (49.3 ± 4.4 mm versus 54.9 ± 4.7 mm, $P<0.001$) and a higher E/E' ratio (7.1 ± 2.0 versus 5.5 ± 1.1 , $P\leq0.001$) compared with athletes with physiological LVH. A small proportion (13.3%) of athletes with mild concentric HCM revealed an LVEDD of >54 mm, 66.7% had a septal E' of ≥0.09 m/s and 93.3% had a lateral E' ≥0.09 m/s. All 15 athletes showed an average E/E' of <12 and 87% had a normal left atrial dimension. Receiver operating characteristic curve analysis demonstrated that most structural and functional parameters had poor ability to differentiate between morphologically mild concentric HCM and physiological LVH in athletes (Table 5). Only an LVEDD ≤51 mm and septal E' ≤0.11 m/s showed good discriminating ability (area under the curve >0.8).

Role of Other Investigations

None of the 15 athletes with mild concentric HCM revealed abnormalities on exercise testing. One athlete (6.7%) with mild concentric HCM demonstrated arrhythmias on 24-hour Holter monitoring, namely nonsustained ventricular tachycardia. None of the healthy athletes with physiological LVH demonstrated abnormalities on exercise testing or Holter monitoring.

Athletes with mild concentric HCM obtained a similar percentage predicted pVO_2 compared with athletes with physiological LVH ($113\%\pm22\%$ versus $122\%\pm14\%$, $P=0.057$). Five (33.3%) athletes with mild concentric HCM obtained a pVO_2 of >120% of that predicted compared with 31 (56.9%) athletes with physiological LVH. Four athletes with mild concentric HCM (26.7%) revealed LGE on CMRI compared with none of the athletes with physiological LVH.

Discussion

Hypertrophic cardiomyopathy is generally characterized by reduced functional capacity,^{18,22} and most patients are unable to engage in competitive sport involving high-intensity exercise.²³ However, several reports in the literature have described affected individuals capable of extraordinary feats of athletic achievement.⁶⁻⁸ Our knowledge of the ability of these individuals to perform at such a high level, and whether their phenotype differs from ordinary (sedentary) patients, is limited. Furthermore, the superadded effect of cardiac loading conditions associated with exercise itself on the HCM phenotype is also unknown. The differentiation of physiological LVH from morphologically mild HCM is challenging, and an erroneous diagnosis has potentially serious consequences. When faced with such a dilemma, the differentiation places considerable reliance on other structural and functional LV parameters, assuming that they are similar to those in sedentary HCM patients. The present study provided a unique opportunity for examining the HCM phenotype in affected young asymptomatic athletes.

Differences in Athletes With HCM and Sedentary HCM Patients

Compared with sedentary HCM patients, athletes with HCM revealed milder LVH and the apical variant of the condition in more than a third of the cohort, both of which were independent predictors of athletic status (Figure 3). The apical variant of HCM could also be classified into the mild LVH category because the hypertrophy is localized to a small segment of the left ventricle and may not affect the dynamics of the chamber as much as more generalized hypertrophy.

Similar to studies comparing healthy athletes with sedentary controls, athletes with HCM showed larger LV cavity dimensions compared with sedentary HCM patients. Indeed, only a small proportion of sedentary HCM patients (3%) showed dimensions exceeding 54 mm compared with 14.2% of the athletes with HCM. It is generally recognized that a dilated left ventricle is usually observed in the end stages of HCM in $\approx5\%$ of patients and is associated with poor contraction and functional capacity.²⁴ In the case of athletes with HCM, the enlarged LV cavity is likely to represent physiological adaptation to increased cardiac workload associated

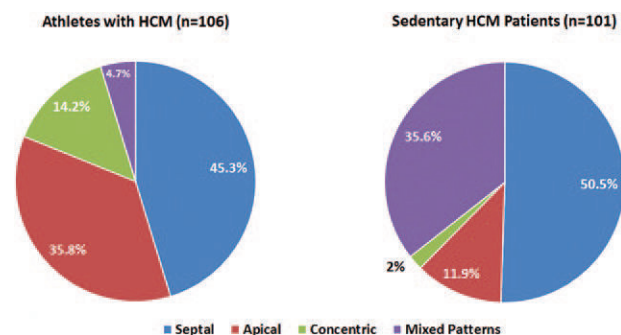


Figure 2. Differences in LVH patterns between athletes with HCM and sedentary HCM patients. HCM indicates hypertrophic cardiomyopathy; and LVH, left ventricular hypertrophy.

Table 4. Univariable and Multivariable Predictors of Athletic Status in Patients With HCM

	Univariate	P Value	Multivariate	P Value
Age, per year	0.97 (0.93–1.01)	0.103		
Sex (female/male)	0.55 (0.19–1.56)	0.259		
Family history of hypertrophic cardiomyopathy/sudden cardiac death	0.40 (0.22–0.71)	0.002		
Murmur on examination	0.39 (0.20–0.77)	0.006		
Heart rate, per 10 bpm	0.61 (0.47–0.79)	<0.001		
T-wave inversion	4.8 (1.55–14.9)	0.007		
ST elevation	1.80 (1.03–3.14)	0.039	3.11 (1.19–8.11)	0.020 (4)
ST depression	1.73 (1.0–3.0)	0.052		
QRS fragmentation	0.44 (0.24–0.81)	0.009	0.31 (0.10–0.91)	0.033 (5)
LV end diastolic diameter, mm	1.08 (1.03–1.12)	0.001		
Maximum LV wall thickness, mm	0.88 (0.83–0.94)	<0.001	0.86 (0.75–0.98)	0.023 (2)
Systolic anterior motion of anterior mitral valve leaflets (at rest)	0.28 (0.12–0.66)	0.004		
LV outflow tract gradient >30 mm Hg (at rest)	0.15 (0.03–0.69)	0.015		
Mitral <i>E/A</i>	1.97 (1.11–3.49)	0.020		
Average <i>E/E'</i>	0.74 (0.66–0.83)	<0.001		
Mitral regurgitation (>mild)	0.07 (0.02–0.23)	<0.001	0.16 (0.04–0.72)	0.017 (3)
LV hypertrophy pattern		<0.001		<0.001 (1)
Apical versus mixed	22.8 (7.3–71.18)	<0.001	21.81 (4.77–99.81)	<0.001
Septal versus mixed	6.78 (2.46–18.7)	<0.001	9.15 (2.17–38.63)	0.003
Concentric versus mixed	54 (9.4–309.8)	<0.001	44.79 (4.55–441.37)	0.001
Nonsustained ventricular tachycardia on 24 h Holter	0.32 (0.13–0.75)	0.009		
Documented atrial fibrillation	0.09 (0.02–0.38)	0.001		

In the multivariable *P* value column, the numbers in parentheses indicate the order of significance of the independent variables selected in the final forward likelihood ratio model. HCM indicates hypertrophic cardiomyopathy; and LV, left ventricular.

with exercise. The preservation of radial contraction, longitudinal systolic function, and high pVO_2 favors a physiological process.

Most athletes with HCM showed normal indices of diastolic function according to conventional cut-off values on

Tissue Doppler imaging. Only 2% of athletes with HCM revealed left ventricular outflow tract obstruction at rest. Thus, the combination of a larger LV volume, normal LV diastolic function, and absence of dynamic left ventricular outflow tract obstruction likely facilitate the augmentation of stroke

Table 5. Receiver Operating Characteristic Analysis Evaluating Conventional Structural and Functional Echocardiographic Parameters for Distinguishing Physiological LVH in Healthy Athletes (n=55) From Pathological LVH in Athletes With Mild Concentric HCM (n=15)

Variable	Area Under the Curve	Sensitivity, %	Specificity, %	P Value
LVEDD ≤ 51 mm*	0.819	72.7	81.8	<0.001
LVEDD ≤ 54 mm†	0.819	81.8	61.8	
Average <i>E/E'</i> >6.6*	0.653	60.0	79.0	0.171
Average <i>E/E'</i> >12†	0.653	0.0	100	
Relative wall thickness >0.45*†	0.760	81.8	65.4	0.013
Lateral <i>E'</i> ≤ 0.15 m/s*	0.700	90.0	47.4	0.043
Lateral <i>E'</i> ≤ 0.09 m/s†	0.700	20.0	100	
Left atrium ≤ 38 mm*	0.602	72.7	45.5	0.263
Left atrium ≤ 40 mm†	0.602	90.9	23.6	
Septal <i>E'</i> ≤ 0.11 m/s*	0.877	88.9	68.4	<0.001
Septal <i>E'</i> ≤ 0.09 m/s†	0.877	55.6	100	
Mitral A wave >0.40*	0.771	100	50.0	<0.001
Mitral A wave >0.46†	0.771	72.7	67.3	

HCM indicates hypertrophic cardiomyopathy; LVEDD, left ventricular end diastolic dimension; and LVH, left ventricular hypertrophy.

*Value calculated by Youden's Index as best compromise between sensitivity and specificity.

†Sensitivity and specificity at traditional cut-off values.

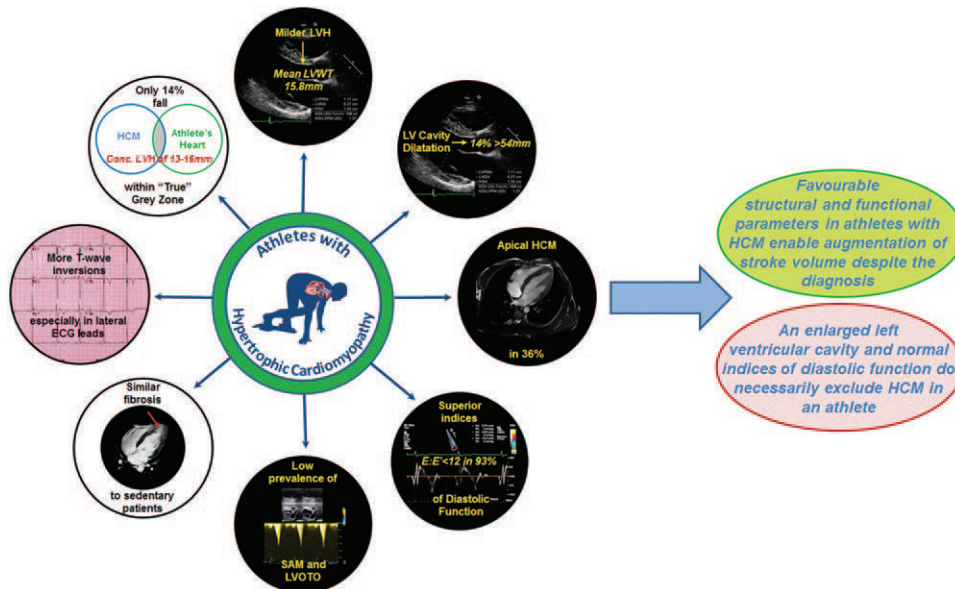


Figure 3. The clinical profile of athletes with hypertrophic cardiomyopathy (HCM). This illustration summarizes the electrocardiographic, structural, and functional characteristics that differ between athletes with HCM and sedentary HCM patients. A combination of these features may explain why athletes with HCM are able to compete in sporting activities at an extraordinarily high level, in contrast to most patients with HCM who show functional limitation. Only a minority of athletes with HCM fall within the true gray zone between physiological and pathological left ventricular hypertrophy (LVH); these individuals may exhibit left ventricular (LV) cavity dilatation and normal indices of diastolic function, which cannot therefore be used to exclude the diagnosis of HCM in an athlete in isolation. LVWT indicates left ventricular wall thickness.

volume, which is the major determinant of peak exercise capacity in HCM in the presence of adequate LV filling.^{25,26}

Myocardial fibrosis is a commonly cited explanation for a noncompliant left ventricle and impaired myocardial relaxation.²⁷ However, a similar proportion of athletes with HCM and sedentary patients demonstrated LGE on CMRI. These results underscore the importance of CMRI as a diagnostic tool in athletes with a high index of suspicion for HCM. At the same time, however, our results suggest that superior methods of detecting generalized fibrosis are necessary to study the pathophysiology of HCM.²⁸ It is also possible that athletes with HCM had a lower ischemic burden because of the absence of severe LVH and mechanical LV obstruction, which enabled more exercise, despite a similar magnitude of scarring.

Differentiation of Athlete's Heart From Morphologically Mild HCM

Previous studies have reported several parameters, which are now regarded as good discriminators between athlete's heart and morphologically mild HCM, including LV cavity dimension, indices of LV diastolic function, and left atrial dimension.^{2,3,11,29} A recent report suggested an LV cavity dimension of >54 mm to be a particularly good discriminator, favoring physiological LVH over HCM with both a sensitivity and specificity of 100%.⁴ However, these studies are limited by the fact that they relied on data from sedentary HCM patients, who do not provide an appropriate comparison group.

Our observations suggest that the vast majority of athletes with HCM exhibit a maximal left ventricular wall thickness of ≥ 16 mm and nonconcentric patterns of LVH, which would be diagnostic of HCM based on current algorithms for differentiating physiological LVH from morphologically mild HCM.

Indeed, only 14% of athletes with HCM seem to fall into the conventional and often challenging gray zone of mild (13–16 mm), concentric LVH. Among athletes in this gray zone, our analysis revealed that an LV cavity ≤ 51 mm favoring a diagnosis of HCM offers the best compromise between sensitivity and specificity when discriminating physiological from pathological LVH. A value of ≤ 54 mm had better sensitivity, but at the expense of higher false-positive results (Table 5). In contrast with a recent report,⁴ our study failed to identify any cut off value for left atrial diameter that adequately distinguished physiology from pathology. Indices of diastolic function were normal in most athletes with HCM and should not be used in isolation to exclude HCM in an athlete with LVH.

This study reaffirms the value of the ECG in diagnosing HCM in athletes. We concede that our cohort is heavily biased because ECG anomalies, particularly T-wave inversion, were the primary reason for referral after preparticipation screening. The fact remains, however, that 96% of athletes and 84% of patients with HCM exhibited pathological T-wave inversion, the great majority of which involved the lateral leads. Moreover, 57% of athletes with HCM exhibited ST-segment depression and almost a quarter revealed pathological Q-waves. In contrast, none of the athletes with physiological LVH demonstrated deep T-wave inversion in the lateral leads, ST-segment depression, or pathological Q-waves. None of the athletes with HCM exhibited isolated voltage criterion for LVH, reinforcing the message that large QRS complexes in isolation are not necessarily indicative of quiescent HCM.⁹

Exercise testing and Holter monitoring would have facilitated the diagnosis in only 19% of athletes with HCM. Contrary to a previous publication,¹⁸ 25% of athletes with HCM achieved a $pV_{O_2} > 120\%$ of predicted. In line with a recent publication,³⁰ the value of CMRI is underscored by the

detection of LGE in a third of athletes with HCM, in addition to its ability to delineate the pattern of LVH.

Clinical Implications

Our results have significant practical implications for differentiating physiological LVH from morphologically mild HCM. Most athletes with HCM exhibit features which would facilitate the diagnosis of HCM if current diagnostic algorithms are applied. Among the small proportion of athletes with mild concentric LVH of 13 to 16 mm, an increased LV cavity size, normal diastolic function, or superior indices of functional capacity should not be used in isolation to exclude HCM. An exercise test can help facilitate the diagnosis in a fifth of cases, and CMRI is diagnostic in one third of cases after ECG and echocardiography. In athletes with a high index of suspicion for HCM because of the presence of LVH and coexisting repolarization anomalies, the assessing physician should use the whole complement of noninvasive cardiac tests to assist the diagnosis. Although not assessed specifically in this study, detraining,^{8,31} familial evaluation, and genetic testing, though challenging, may also have important additional roles.

Limitations

The authors recognize that a small proportion of athletes with HCM may not have been identified during the screening process given the heterogeneity and aged-related penetrance of the condition, resulting in ascertainment bias. However, the use of history, ECG, and echocardiography to screen all athletes coupled with repeat interval screening at later dates should have limited this number to a minimum. In view of the small number of athletes with mild concentric LVH, it was not feasible to confidently identify independent discriminators of pathological versus physiological LVH using logistic regression. The authors recognize the limitations of receiver operating characteristic curve analysis in isolation and acknowledge the need for large, purposefully built cohorts that aim to identify independent predictors of HCM in athletes with mild concentric LVH.

Conclusions

Athletes with HCM exhibit qualitatively similar physiological cardiac adaptation to normal healthy athletes. An important minority of athletes with HCM (14%) constitute the conventional gray zone of mild (13–16 mm) concentric LVH. In such cases, a large LV cavity or normal indices of diastolic function alone are insufficient to differentiate pathological from physiological LVH. Conventional echocardiographic parameters should be complemented by ECG, exercise stress testing, and CMRI to minimize the risk of false reassurance.

Acknowledgments

We thank Cardiac Risk in the Young for providing portable echocardiography equipment and ECG machines used in the United Kingdom.

Sources of Funding

Professor Sanjay Sharma and Dr Nabeel Sheikh received research grants from Cardiac Risk in the Young (CRY) and the British Heart Foundation. Dr Papadakis and Dr Malhotra were funded by research

grants from CRY. Studies on French athletes were supported by grants from the Club des Cardiologues du Sport and French Ministry of Health and Sport.

Disclosures

None.

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CLINICAL PERSPECTIVE

Compared with sedentary hypertrophic cardiomyopathy (HCM) patients, athletes with HCM exhibit a higher prevalence of T-wave inversion, milder left ventricular hypertrophy (LVH), larger cavity dimensions, and superior indices of diastolic function. Fourteen percent of athletes with HCM have an left ventricular end diastolic dimension >54 mm and 93% have an E/E' of <12. Furthermore, over one-third (36%) of athletes with HCM reveal an apical pattern of LVH, and most (86%) have a magnitude and pattern of hypertrophy consistent with a diagnosis of HCM using conventional definitions. Only a small number (14%) fall within the true gray zone of mild (13–16 mm) concentric LVH. In this small but significant subgroup, conventional discriminators between athlete’s heart and HCM, particularly a large left ventricular cavity or normal indices of diastolic function, are in isolation insufficient to differentiate physiological LVH from HCM. Therefore, when faced with an athlete falling within the gray zone of LVH, physicians involved in athlete preparticipation screening programs should complement echocardiography with ECG, exercise stress testing, and cardiac MRI before making a diagnosis.

3. Apport des nouvelles techniques de déformations myocardiques dans les CMH

Lors du travail précédent, nous avons démontré que le diagnostic de CMH était encore plus difficile chez l'athlète compte tenu de caractéristiques échocardiographiques moins pathologiques. Nous avons également démontré précédemment que l'échocardiographie est souvent prise en défaut dans le diagnostic de cardiopathie chez les athlètes avec ondes T négatives. Mais dans ces études nous n'avions utilisé que des paramètres échocardiographiques de routine, sans intégrer les nouvelles techniques d'étude des déformations myocardiques.

Nous avons donc cherché à déterminer si l'utilisation des techniques de déformations myocardiques (2D strain) était capable d'apporter des arguments supplémentaires permettant de mieux différencier HVG physiologique et pathologique.

Dans ce chapitre, nous avons dans un premier temps inclus des CMH non sportives afin de mieux valider l'intérêt du 2D strain dans l'étude des CMH. Le principal objectif des études décrites dans ce chapitre était de mieux expliciter les causes d'altération du 2D strain dans les CMH. Pour discuter du rôle de la post charge sur les paramètres de déformations myocardiques nous avons également inclus un autre type de remodelage hypertrophique pathologique, à savoir l'HVG en lien avec une surcharge en pression liée à un rétrécissement aortique.

Nous avons par ailleurs essayé de valider l'utilisation de l'échocardiographie d'effort comme outil de diagnostic et de pronostic dans la CMH.

3.1.Déformations myocardiques et caractérisation tissulaire

Dans une première étape, nous avons cherché à déterminer si le 2D strain était capable de détecter la fibrose macroscopique. Cela avait déjà été démontré dans des études antérieures^{36,37}, mais nous avons souhaité valider ces données préliminaires en utilisant une méthode originale de fusion des données échocardiographiques et d'IRM. En effet, la présence de rehaussement tardif en IRM est un élément diagnostique majeur pour différencier les 2 types de remodelages hypertrophiques. L'échocardiographie étant un outil plus accessible que l'IRM il nous est apparu intéressant d'essayer de valider la place du 2D strain comme outil de dépistage de fibrose. Ceci pourrait avoir comme intérêt de mieux sélectionner les sujets nécessitant une IRM myocardique.

Apport du candidat dans ce travail

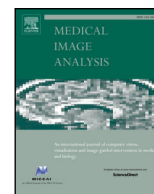
Conception du projet, collaboration avec une équipe d'ingénieurs. Réalisation des inclusions, réalisation des échocardiographies, relecture des échocardiographies et des IRM. Validation de l'ensemble des étapes cliniques. Relecture et correction du manuscrit.

RESUME

Objectifs : Les informations apportées par l'échocardiographie et l'IRM pour la caractérisation des CMH sont complémentaires. En effet l'échocardiographie permet d'avoir facilement accès aux données mécanistiques de déformations myocardiques. L'IRM est capable de fournir des données de caractérisation tissulaire grâce à l'étude du rehaussement tardif (LGE), un outil non invasif de détection de la fibrose myocardique. L'objectif de cette étude était de mieux interpréter les données de 2D strain grâce à la fusion avec les données de LGE.

Méthodes et résultats : Des méthodes de recalage et de fusion permettant d'amener dans un même référentiel des images IRM et échographiques ont été utilisées. Les méthodes proposées ont reposé sur deux processus principaux : l'alignement temporel et le recalage spatial. Les dimensions temporelles des images ont été synchronisées par une méthode de déformation temporelle dynamique adaptative permettant de compenser les modifications temporelles non-linéaires entre les différentes acquisitions. Pour le recalage spatial, des méthodes iconiques ont été développées pour corriger les artefacts de mouvements dans les séquences ciné-IRM, afin de recaler les séquences ciné-IRM avec les séquences IRM de rehaussement tardif. D'autre part, une méthode basée sur les contours a été utilisée pour prendre en compte des acquisitions échographiques multi-vues. Cette analyse a permis d'évaluer le strain régional en tant qu'indicateur de présence locale de fibrose. 28 patients ont été analysés, un bon alignement entre les données de 2D strain et de LGE a été obtenu dans 306/330 segments ventriculaires gauches. Les régions correctement alignées ont été utilisées pour évaluer la capacité du pic de strain et du délai au pic de contraction à prédire la présence de fibrose. Nous avons démontré que les segments myocardiques avec fibrose avaient des valeurs de strain plus altérées et également un délai de contraction plus prolongé.

Conclusion : L'altération des déformations myocardiques échographiques retrouvées dans la CMH peut en partie être expliquée par la présence de fibrose macroscopique.



Registration of dynamic multiview 2D ultrasound and late gadolinium enhanced images of the heart: Application to hypertrophic cardiomyopathy characterization



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ARTICLE INFO

Article history:

Received 26 December 2014

Revised 27 October 2015

Accepted 27 October 2015

Available online 10 November 2015

Keywords:

Multimodal image registration

Cardiac ultrasound

Speckle tracking echocardiography

Late gadolinium-enhanced magnetic resonance

Hypertrophic cardiomyopathy

ABSTRACT

Describing and analyzing heart multiphysics requires the acquisition and fusion of multisensor cardiac images. Multisensor image fusion enables a combined analysis of these heterogeneous modalities. We propose to register intra-patient multiview 2D+t ultrasound (US) images with multiview late gadolinium-enhanced (LGE) images acquired during cardiac magnetic resonance imaging (MRI), in order to fuse mechanical and tissue state information. The proposed procedure registers both US and LGE to cine MRI. The correction of slice misalignment and the rigid registration of multiview LGE and cine MRI are studied, to select the most appropriate similarity measure. It showed that mutual information performs the best for LGE slice misalignment correction and for LGE and cine registration. Concerning US registration, dynamic endocardial contours resulting from speckle tracking echocardiography were exploited in a geometry-based dynamic registration. We propose the use of an adapted dynamic time warping procedure to synchronize cardiac dynamics in multiview US and cine MRI. The registration of US and LGE MRI was evaluated on a dataset of patients with hypertrophic cardiomyopathy. A visual assessment of 330 left ventricular regions from US images of 28 patients resulted in 92.7% of regions successfully aligned with cardiac structures in LGE. Successfully-aligned regions were then used to evaluate the abilities of strain indicators to predict the presence of fibrosis. Longitudinal peak-strain and peak-delay of aligned left ventricular regions were computed from corresponding regional strain curves from US. The Mann–Withney test proved that the expected values of these indicators change between the populations of regions with and without fibrosis ($p < 0.01$). ROC curves otherwise proved that the presence of fibrosis is one factor amongst others which modifies longitudinal peak-strain and peak-delay.

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1. Introduction

The heart is a complex organ involving and coupling different physical phenomena that can be assessed using multisensor cardiac imaging. The fusion of such multisensor information enables the description of heart multiphysics and the assessment of relationships between cardiac image modalities (e.g. complementarity or redundancy). For this purpose, image registration is required. In this work, we propose a method to register intra-patient cardiac 2D ultrasound (US) with late gadolinium-enhanced (LGE) magnetic resonance imaging (MRI).

Indeed, dynamic 2D US is the gold standard modality to assess myocardial strain and LGE provide information about myocardial viability. But the relationship between these descriptors remain unclear. We aim to fuse these modalities to evaluate the alteration of US strain with regards to the presence of fibrosis in LGE. We propose to consider cine MRI as an intermediate image for the registration process to overcome the challenges of the multimodal registration of 2D US and 3D LGE.

LGE and 2D US images are acquired following multiple views (e.g. short axis, four-chamber, two-chamber) of the left ventricle (LV). US views, however, usually do not match MRI views. As a consequence, some structures are not well represented (e.g. the apical zone in MRI short axis view) or are distorted due to field-of-view constraints (e.g. the apical zone in apical long axis view US using transthoracic probes). Moreover, their multimodal nature, difference in temporal

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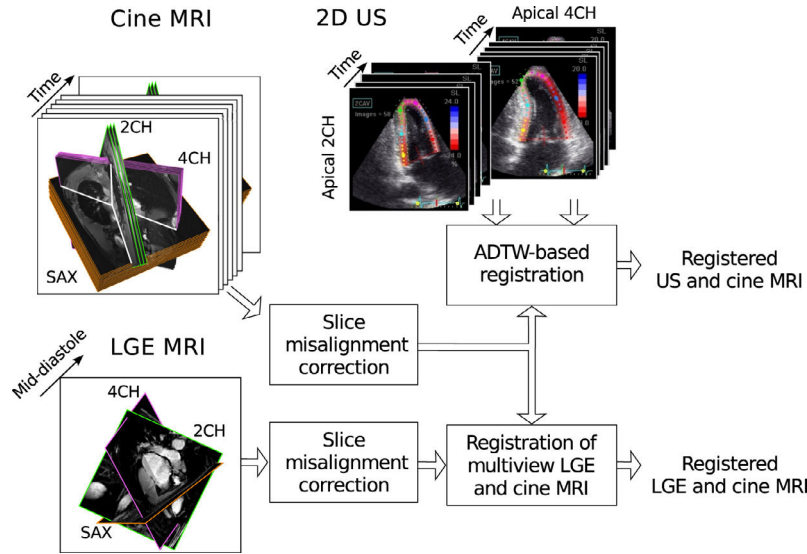


Fig. 1. Image registration framework of intra-patient 2D US and LGE MRI. Cine MRI is used as intermediary modality. It is set as the reference image.

and spatial resolution (dynamic 2D US vs static 3D LGE), the low US image quality and the presence of enhanced regions in LGE also hinder their registration.

Cine MRI is a good intermediate between US and LGE because US and cine are dynamic and because LGE is close to cine. On one hand, a dynamic registration approach of dynamic US and cine images yields a more robust spatial alignment, because the information concerning LV deformation is exploited. However, these images are not simultaneously acquired and cardiac dynamics change over time in a non-linear fashion (e.g. longer contraction and shorter relaxation). Consequently, this registration requires the synchronization of US and cine images. On the other hand, cine and LGE are acquired during the same MRI examination; thus, a rigid registration approach can be considered to align them. Nevertheless, they are acquired during multiple heartbeats, which results in potential slice misalignment. Then, appropriate similarity measures must be selected to correct for slice misalignment and to register LGE and cine MRI.

We propose an intra-patient registration procedure of both LGE and 2D US, with cine MRI. This aims to improve US-to-LGE registration by exploiting LV deformation. The registration procedure has been divided into three steps: (i) correction of slice misalignment in LGE and cine MRI, (ii) registration of LGE and cine MRI, and (iii) dynamic registration of US and cine MRI. One contribution of this paper concerns selecting the best similarity measure to correct and register LGE and cine MRI. US-to-cine registration relies on the Dynamic Time Warping procedure (DTW) to compute a spatiotemporal similarity measure from the Fourier descriptors of input LV contours (Tavard et al., 2014). The DTW is an effective procedure to match dynamic time variations between time series (e.g. due to contraction and elongation of cardiac phases); however, it can lead to the presence of artifacts in the synchronization of cardiac dynamics. In this paper, we propose to adapt the DTW procedure to compute a coherent warping of cardiac phases in US and cine images.

The proposed registration method is presented in the next section in three steps: slice misalignment correction of LGE and cine MRI (Section 2.1), registration of LGE and cine MRI (Section 2.2), and dynamic registration of 2D US and cine MRI (Section 2.3). The evaluation of image registration procedures is presented in Section 3. This focuses on selecting the best similarity measure to correct LGE slice misalignment and to align LGE and cine MRI, and on the evaluation of US-to-LGE registration. Section 3.4 is dedicated to an application of the proposed registration workflow. US and LGE fusion enabled to study if the alteration of strain-derived indicators is caused by the

presence of fibrosis in patients with hypertrophic cardiomyopathy (HCM). The conclusion and perspectives are presented in Section 4.

2. Methods

Fig. 1 presents the proposed registration framework. The cine short axis view (SAX) image is used as the reference image to register both LGE and US. The acquisition of US, cine and LGE is described in Section 3.1. The registration procedure corrects for slice misalignment in LGE and cine MRI and then registers corrected multiview images. US and corrected cine-SAX are then aligned using a registration approach based on an adapted DTW (ADTW) procedure. Below we present these three steps.

2.1. Slice misalignment correction of LGE and cine MRI

MRI systems image one cardiac phase during multiple heartbeats and, even under breath-hold acquisitions, patient physiological motion (mainly breathing) cannot be completely avoided, resulting in rigid slice misalignment (Prieto, 2013; McLeish et al., 2002). Thus, slice misalignment must be corrected to exploit the information that they contain. The registration of multiview cine images has been used to find the spatial transformation per slice that corrects for out-of-plane and/or in-plane misalignments (Carminati et al., 2012; Elen et al., 2010; Slomka et al., 2007; Lötjönen et al., 2005). (Slomka et al., 2007) proposed a correction approach with two registration steps. In the first step, two-chamber view (2CH) and four-chamber view (4CH) images, each with only one slice, are registered. In the second step, they are fixed to correct each slice in the SAX image. (Elen et al., 2010) used a combined approach that corrects input slices in a single registration. They also reported a comprehensive study of similarity measures showing that absolute voxel differences and normalized mutual information (NMI) perform the best. Few works have been reported for LGE correction. (Wei et al., 2013) corrected for in-plane misalignments in LGE using a metric including both, iconic similarity and continuity of the heart. This requires the delineation of heart structures which is difficult in the presence of fibrosis/scar.

We use a sequence of three registration steps to correct for slice misalignments in 2CH, 4CH and SAX cine/LGE MRI. In the first step, the 4CH image is corrected using the median slice of 2CH as the reference image. In the second step, the corrected 4CH image is used to correct the 2CH image. In the third step, the SAX image is corrected

using corrected 2CH and 4CH as the reference image. Each slice is corrected with a registration procedure that exploits the image profiles resulting from its intersection with the slices of the other view(s). The registration optimizes the similarity between Gaussian-smoothed profiles (kernel size is equal to slice thickness), with regards to the slice transformation parameters (μ). As in [Slomka et al. \(2007\)](#), the relative rotation of the 2CH and 4CH slices was not considered, due to a lack of adequate spatial information in the 2CH–4CH intersection. Thus, we use $\mu = (x_1, x_2)^T$ in steps 1 and 2 which corresponds to an in-plane translation. In step 3, we use $\mu = (x_1, x_2, \sigma_1, \sigma_2)^T$ which corresponds to an in-plane translation and an anisotropic scaling in the two axes of the slice. This scaling is the geometrical equivalent of a plane tilt.

The registration of each slice was applied using a simplex optimization and linear interpolation. The NMI metric was used in the case of cine correction ([Elen et al., 2010](#)). Concerning LGE, the most appropriate similarity measure was selected using the protocol of [Skerl et al. \(2006\)](#) (Section 3.2). We evaluated the mean square (MS), normalized correlation (NC), Viola-Wells mutual information (VWMI), Mattes MI (MMI) and NMI metrics. LGE is a modality containing information concerning the structure of myocardial tissue; thus, it seems appropriate to exploit this information to compute similarity. Hence, we evaluated the local entropy representation of LGE images proposed by [Wachinger and Navab \(2012\)](#). The MS metric of these structural images (MS-S) is used to measure the similarity between LGE slices. The local entropy image is computed for each slice by calculating, for each voxel, the entropy of its neighborhood. For this, we used a 2D neighborhood of 11×11 .

2.2. Registration of LGE and cine MRI

Following the correction of slice misalignment, the multiview LGE image is rigidly registered to the multiview cine image. Assuming all cine views having the same temporal resolution, this optimization is defined as:

$$\tilde{\mu} = \arg \min_{\mu} \sum_{v \in V} \mathcal{M}(\tilde{I}^{\text{cine},v}(\tau^{\text{LGE}}), T_{\mu}(\tilde{I}^{\text{LGE},v})) \quad (1)$$

where $\tilde{\mu} \in \mathbb{R}^6$ is the vector of optimal rigid transformation parameters (translation, rotation), $v \in \{\text{SAX}, \text{4CH}, \text{2CH}\}$ is a given view, \mathcal{M} is a similarity measure, $\tilde{I}^{\text{cine},v}$ is the corrected v -view cine image sequence, τ^{LGE} is the cardiac phase aligning cine and LGE images over time, T_{μ} is a rigid transform and $\tilde{I}^{\text{LGE},v}$ is the corrected v -view LGE image. τ^{LGE} is selected as the closest phase in cine-SAX computed from the TriggerTime (0018,1060) and the average heart rate (0018,1088) DICOM tags from both acquisitions.

The rigid registration framework was implemented using a regular gradient descent optimization and a linear interpolation. However, the best similarity measure must be selected due to the intensity heterogeneity between cine and LGE caused by the accumulation of contrast agent in fibrous tissues: a myocardium with fibrosis appears as homogeneous tissue in cine, while it presents bright regions in LGE. [Hennemuth et al. \(2008\)](#) presented a workflow enabling the alignment of stacked slices and the registration of contrast-enhanced images. [Cordero-Grande et al. \(2012\)](#) presented an analogous method to correct and register LGE and cine. Nevertheless, they only accounted for in-plane motion, supposed that LGE was acquired at end-diastole (while routinely at mid-diastole), and the pertinence of using the local entropy representation of input images proposed by [Wachinger and Navab \(2012\)](#) was not evaluated. Thus, we evaluated MS-S, NC, VWMI, MMI and NMI metrics using the protocol of [Skerl et al. \(2006\)](#) (Section 3.2). In this case, local entropy images were computed using a 3D neighborhood of $11 \times 11 \times 11$ after volume re-sampling.

2.3. Dynamic registration of US and cine MRI

The dynamic registration of multiview 2D US with cine MRI aims to align these modalities over time, to obtain the pose of US planes and to align depicted cardiac structures. However, the low quality of US images makes it difficult to carry out this task. Moreover, given the field-of-view constraints of US transducers, output geometries do not exactly fit those in cine. ECGs have been used to align these images over time, enabling for one US instant to be located between two cine instants ([Zhang et al., 2006](#); [Huang et al., 2007](#)). Nevertheless, the sequence of images in cine MRI is acquired during multiple heartbeats, ECGs are deformed because of the strong magnetic field and are not always stored (beyond time instants). Concerning their spatial registration, stereotactic (used in sterotactic surgery) ([Huang et al., 2009](#); [Zhang et al., 2006](#)), iconic (using voxel intensities), geometrical (using cardiac structures) ([Tavard et al., 2014](#)) and simulation-based (simulation of one modality from the other) ([Wein et al., 2008](#)) methods have been proposed. A manual alignment step usually precedes an iconic or geometrical registration. Geometrical approaches exploit tracked structures (e.g. the myocardial wall from US), or placed fiducials such as LV papillary muscles, the junction of left and right ventricles ([Savi et al., 1995](#)), the apex and the mitral annulus ([Tournoux et al., 2010](#)). However, it is difficult to correctly mark these fiducials both in multiview 2D images and in 3D volumes.

We use a geometrical approach method that registers dynamic multiview US and cine-SAX in three steps: (i) LV segmentation of both modalities, (ii) ADTW-registration (registration relying on a Dynamic Time Warping procedure with adapted step pattern) ([Betancur et al., 2015](#)), and (iii) alignment of LV contours. In the segmentation step, dynamic LV geometries in cine-SAX and multiview 2D US image sequences are extracted. In the ADTW-registration, US planes are located in cine-SAX spatiotemporal reference. In the contours alignment step, LV geometries from US and cine-SAX that lie in US planes are aligned. The registration and contour alignment steps are illustrated in [Fig. 2](#). They improved the approach of [Tavard et al. \(2014\)](#) by using an adapted step pattern during DTW and a combined optimization of US planes parameters.

2.3.1. LV segmentation

Dynamic LV endocardial contours from multiview 2D US are extracted using Speckle Tracking Echocardiography (STE). On each view, the endocardial border is delineated by an expert at end-systole and tracked using STE analysis. In cine MRI, the dynamic LV endocardial surface is segmented from misalignment compensated cine-SAX using the interactive ITKSNAP implementation of the snake evolution approach ([Yushkevich et al., 2006](#)). Each dynamic slice is stored as an image volume with the z axis being the cardiac phases. The z axis is then interpolated to obtain an isotropic volume. The snake evolution was initialized with spherical surfaces covering LV blood pool along the z axis. The parameters of the front propagation equation governing snake evolution are defined interactively (typical values were 1.0 and 0.3 for force and curvature terms, respectively). The shape of the initial snake is then deformed until the endocardial border is reached. The dynamic LV surface is obtained by stacking the segmentations of all slices.

2.3.2. ADTW-registration

We propose to warp the temporal dimension of input images using a DTW procedure with adapted step pattern (ADTW) ([Betancur et al., 2015](#)). The goal is to perform the nonlinear synchronization of dynamic cardiac acquisitions while constraining the resulting time alignment to be coherent (i.e. consistent with the expected elongation/contraction of cardiac dynamics). Nonlinear synchronization is required because dynamic US and cine-SAX are not simultaneously acquired; thus, cardiac dynamics change nonlinearly (e.g. a longer contraction and a shorter relaxation). The ADTW-registration aims

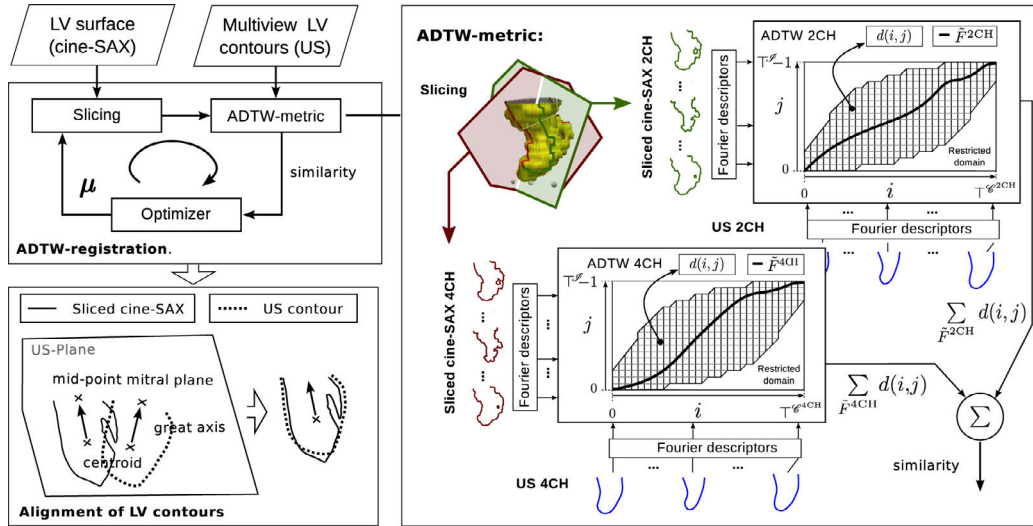


Fig. 2. Dynamic registration of multiview 2D US and cine-SAX. (Left) Input LV surface from cine-SAX and multiview LV contours from US are registered in two steps. First, the ADTW-registration procedure locates US planes in the cine-SAX spatiotemporal reference. Second, multiview US contours are aligned with those resulting from slicing the LV surface with output US planes. (Right) Spatiotemporal metric optimized during the registration procedure: cardiac phases of US-2CH and US-4CH are warped to those of cine-SAX using the ADTW procedure that provides both, the temporal alignment (\tilde{F}^{2CH} and \tilde{F}^{4CH}) and their similarity.

at localizing the acquisition planes of multiview US images into the cine-SAX coordinate system, both in time and in space (Fig. 2(top-left)). ADTW is used to measure the spatiotemporal similarity between LV contours from US and corresponding contours extracted by slicing the LV segmentation from cine-SAX with the US planes. Let $\mathcal{S}(\tau^{\mathcal{S}})$ be the dynamic LV surface from cine-SAX with $\tau^{\mathcal{S}} \in \{0, \dots, T^{\mathcal{S}} - 1\}$ a cardiac phase. Also, let μ^v be the parameters defining an acquisition plane in a 3D space for the US image at view $v \in \{2CH, 4CH\}$, namely its normal vector and origin. The output contour after slicing $\mathcal{S}(\tau^{\mathcal{S}})$ with this plane is noted as $\mathcal{S}^{\mu^v}(\tau^{\mathcal{S}})$. This contour is made up of ordered points (e.g. clockwise) lying in the plane.

After slicing, the spatiotemporal similarity measure is computed in two steps (Fig. 2(right)): first, dynamic LV contours are encoded using their Fourier descriptors (FDs); second, encoded contours are aligned over time using the ADTW and their similarity is computed. Fourier descriptors are a well-known approach to encoding planar shapes (Gonzales and Woods, 2002). They enable to measure the similarity between LV contours weighting the contribution of their rough, medium or fine details. We force these descriptors to be rotation and translation invariant because we are interested in finding only the US planes parameters. Thus, only their norm is used (rotation invariance) and the norm of the first descriptor is set to zero (translation invariance).

The proposed ADTW-registration procedure computes the optimal set of US planes parameters ($\tilde{\mu}$). Let $\tilde{F}^v(k) = (\tilde{i}(k), \tilde{j}(k))$ be an optimal warping time curve between a LV contour from US (\mathcal{C}^v) and \mathcal{S}^{μ^v} . $\tilde{F}^v(k)$ is the ordered sequence of time instant tuples that best aligns their time axes, the first tuple being (0,0) and the last tuple being $(T^{\mathcal{C}^v}, T^{\mathcal{S}})$. The optimal set of US planes parameters ($\tilde{\mu}$), is given by:

$$\tilde{\mu} = \arg \min_{\mu} \sum_{v} \sum_{k=0}^{K-1} d(\mu^v; \tilde{F}^v(k)) \cdot w^v(k),$$

with $\mu = \bigcup_{v} \mu^v$, $\tilde{F}^v(k) = (i(k), j(k))$, (2)

where K is the length of \tilde{F}^v , $w^v(k)$ is a nonnegative weight and $d(\mu^v; \tilde{F}^v(k))$ is the distance between the LV contour from US at the i th time instant and the LV contour from cine-SAX at the j th time

instant, defined as:

$$d(\mu^v; i, j) = \sum_{\ell=0}^{L-1} \frac{1}{\ell+1} |\hat{\mathcal{C}}^v(i, \ell) - \hat{\mathcal{S}}^{\mu^v}(j, \ell)|, \quad (3)$$

where L is the number of FDs, $\hat{\mathcal{C}}^v(i, \ell)$ is the ℓ -th FD of \mathcal{C}^v at instant i ($i \in \{0, \dots, T^{\mathcal{C}^v}\}$), and $\hat{\mathcal{S}}^{\mu^v}(j, \ell)$ is the ℓ -th FD of \mathcal{S}^{μ^v} at instant j ($j \in \{0, \dots, T^{\mathcal{S}}\}$). We proved in Betancur et al. (2013) that $L = 60$ favors the influence of rough and medium shape details that these geometries contain.

The optimal time warping curve \tilde{F}^v is computed using the DTW procedure proposed by (Sakoe and Chiba, 1978; Itakura, 1975). At each iteration, the DTW computes \tilde{F}^v as follows:

$$\tilde{F}^v = \arg \min_{F^v} \sum_{k=0}^{K-1} d(\mu^v; F^v(k)) \cdot w^v(k),$$

with $F^v(k) = (i(k), j(k))$, (4)

where F^v is any time warping curve linking the two extrema tuples, $d(\mu^v; F^v(k))$ is given by Eq. 3, and $w^v(k)$ is a nonnegative weight given by a step pattern. The step pattern lists the horizontal, vertical and diagonal transitions allowed at $F^v(k)$. We selected the symmetric form of this pattern; thus $w^v(k) = 1$ for an horizontal or vertical transition and $w^v(k) = 2$ for a diagonal transition. The pattern is built provided the slope constraint (S^v) that defines the number of transitions in the horizontal, vertical and diagonal direction from $F^v(k)$ (Itakura, 1975).

We adapted S^v to consider the ratio of temporal resolution (r^v) between a given view in US and cine-SAX. The slope constraint limits the maximum and minimum slope of \tilde{F}^v (Sakoe and Chiba, 1978), i.e. the maximum and minimum deformation of the time axes (Fig. 3 shows the effect of this constraint in the deformation of the time axes (\tilde{F}^v). If the slope is not constrained (i.e. $S = 0/0$), then hard deformations are allowed. In contrast, if the slope is constrained (e.g. $S = 1/1$), the resulting curve is smoother. We have limited the nonlinear compression and elongation of cardiac dynamics using the temporal resolution ratio between US and cine-SAX, as follows:

$$S^v = \begin{cases} 1/1, & \text{if } r^v = 1 \\ \frac{1}{2 \cdot (r^v - 1)}, & \text{if } r^v > 1 \end{cases}, \text{ with } r^v = \left\lceil \frac{\max(T^{\mathcal{C}^v}, T^{\mathcal{S}})}{\min(T^{\mathcal{C}^v}, T^{\mathcal{S}})} \right\rceil, \quad (5)$$

Eq. 2 is solved iteratively using a simplex optimization that evaluates a combination of plane parameters at each iteration. The initial

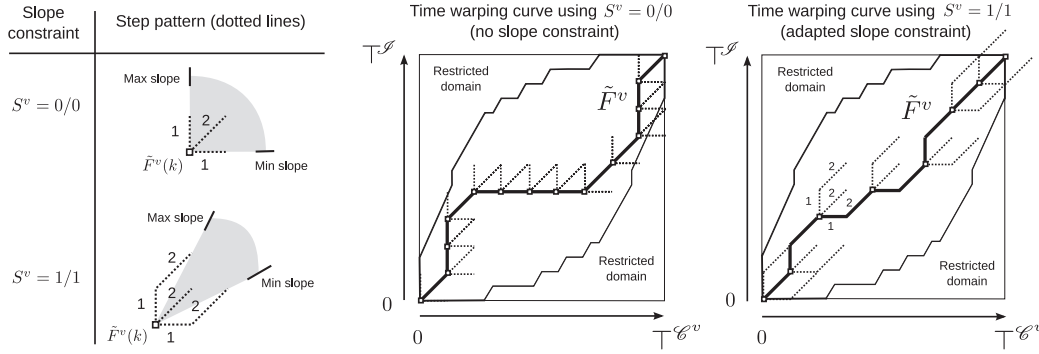


Fig. 3. Effect of the slope constraint (S^v) in the computation of \tilde{F}^v . (Left) Step patterns for $S^v = 0/0$ and $S^v = 1/1$ and their corresponding maximum and minimum slopes. Resulting time warping curves for $S^v = 0/0$ (center) and $S^v = 1/1$ (right). Note the hard deformation caused by the absence of slope constraint (center).

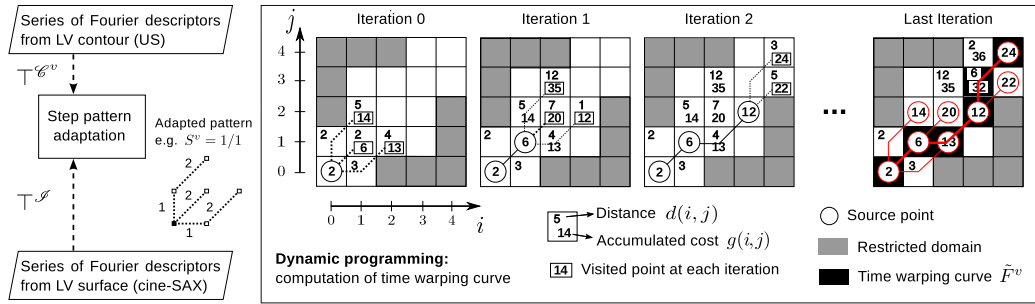


Fig. 4. Adaptive Dynamic Time Warping (ADTW) method: an adapted step pattern ($S = 1/1$ in the example) is used during a dynamic programming procedure to compute the optimal time warping curve (\tilde{F}^v). At each iteration, the procedure adds the tuple with the lowest accumulated cost to a source-tuples list and finds the cost of linking its neighbors using the adapted step pattern, keeping the lowest cost possible. The procedure starts at (0,0) and finishes when the highest tuple is added ((4,4) in the example).

parameters for μ^{2CH} and μ^{4CH} are: a point near to the LV apex used as common origin for the two planes, and the normal vectors of cine-2CH and cine-4CH slices used as US-2CH and US-4CH plane normal vectors, respectively. At each simplex iteration, Eq. 4 is solved using dynamic programming optimization (Fig. 4). This is an iterative procedure that starts at (0,0) and adds new tuples that make up curve segments with minimum accumulated distance, until (T^c, T^v) is added. The domain of candidate tuples is restricted using a combination of Itakura's parallelogram and Sakoe's ribbon (restricted domain in Figs. 2–4) (Tavard et al., 2014).

2.3.3. Alignment of LV contours

LV contours from US and cine-SAX are aligned after posing US planes in cine-SAX coordinates. This is accomplished by translating and rotating US contours such that their great axes and centroids match those of sliced cine-SAX geometries (Fig. 2, bottom-left). The great axis and centroids are computed at the first cardiac phase.

3. Results

In this section, we present a description of the image dataset, the evaluation of the registration process and the insights obtained from fused multisensed LV. A quantitative and qualitative evaluation of the registration process follows. The fusion of multiview US and LGE images is exploited to study the relationship between the presence of fibrosis and the modification of myocardial strain in patients with hypertrophic cardiomyopathy.

3.1. Data

Twenty-eight adult patients with HCM defined as recommended by (Gersh et al., 2011) were enrolled prospectively and consecutively. Patients with history of coronary artery disease or of previous myocarditis were excluded. All patients provided informed consent. US

and MRI were acquired at CHU-Pontchaillou in Rennes, France, in collaboration with CIC-IT 804. This study was part of a systematic database review conducted according to the Declaration of Helsinki and approved under the CNIL (National Commission on Informatics and Liberty of France) number 909378.

Transthoracic echocardiography (TTE) (Vivid 7, GE Healthcare, Horten, Norway) was acquired at rest. The image acquisition frame rate was 60–90 Hz (mean value 75 Hz). For each view, the endocardial wall was delineated by an expert and automatically tracked by the US station using STE analysis. Adequate tracking was verified in real-time and manually corrected, if necessary.

LGE and cine MRI were acquired using cardiac SENSE coils (Philips Achieva®, Philips Medical Systems, Best, The Netherlands). Breath-hold cine (bTFE sequence) and LGE (TFE) were acquired for SAX and long axis views (2CH, 4CH) using retrospective ECG synchronization. Both inversion recovery (IR) and phase-sensitive IR (PSIR) techniques were used to acquire LGE. Thirty cardiac phases were imaged during cine acquisition with 256×256 pixels per slice ($1.25 \times 1.25 \text{ mm}^2$). 12 slices were acquired for SAX and 3–5 for 2CH/4CH (thickness 8–10 mm). Multiview LGE was acquired 5–10 minutes after gadolinium injection (0.1 mmol/kg of Dotarem Guerbet, Roissy, France), at mid-diastole. Typical spatial resolutions were 256×256 pixels ($1.25 \times 1.25 \text{ mm}^2$), 16 slices for SAX and 12 for 2CH/4CH (thickness 5 mm).

3.2. Similarity measures for cine and LGE slice misalignment correction and inter-sequence registration

The online protocol of Skerl et al. (2006) was used to evaluate the performance of similarity measures for (i) LGE slice misalignment correction (intra-sequence registration, LGE-LGE study) and (ii) LGE-to-cine registration (inter-sequence, cine-LGE study). This protocol uses two images with known rigid registration. The rigid transformation aligning them is noted as GT (ground truth). A cardiologist selected a set of patients whose cine and LGE images did not present

slice misalignment. Four patients were found to be suitable for the LGE-LGE study and two patients for the cine-LGE study. These images were used to compute the accuracy (ACC), distinctiveness of the optimum (DO(r)), capture range (CR), number of minima (NOM(r)) and risk of non-convergence (RON(r)) properties of a similarity measure, with r the distance from the position where the similarity measure is the highest (maximum).

The similarity measure properties are calculated from similarity measure values between one image and different transformations of the other. Each transformation is a point in the space of normalized rigid transformation parameters. The normalization avoids the sampling to be biased due to the difference in scale of the translation and rotation components. A set of points is sampled in an hyperball with center GT and radius R . The sampled points lie in N random diametrical lines, each containing M regularly distributed points. For DO and RON two values were retained: near and far the maximum of the similarity measure (e.g. DO near, DO far). These correspond to the value of these properties one step away from the maximum and at 10 mm from the maximum, respectively. They provide information concerning the behavior of the metric when the registration procedure has a good (near) or a rough (far) initialization. For NOM, the average value was used (i.e. an average indicator of the smoothness of the similarity measure). We set $R=3$, $N=50$ and $M=200$. The step size after normalization resulted in 0.165 mm for both studies.

Table 1 presents the properties of MS, MS-S, NC, VWMI, MMI and NMI metrics in the context of LGE-to-LGE registration for four patients (top), and cine-SAX and LGE-SAX registration using two patients (bottom, MS excluded). The properties are reported as mean \pm standard deviation. Four checkerboards depicting the alignment of input images for one patient are presented: two for LGE images (Fig. 5a), and two for cine and LGE images (Fig. 5b). The LGE images used to evaluate these metrics were acquired using the IR technique. Despite the selection of the images by a cardiologist, the accuracy, which relies on a perfect knowledge of GT, must be carefully

interpreted. The similarity measures were implemented with elastix (Klein et al., 2010) using 420,000 samples, 32 histogram bins (MMI, NMI) and 0.4 as Gaussian kernel size in VWMI computation (input images were normalized). The static image sampler of elastix was used.

CR indicator resulted constant and equal to the step size for all tests in Table 1. The definition of CR is rather strict (Skerl et al., 2006). Resulting CR behavior means that at least one metric profile had one local minimum at one step from its global maximum, for all similarity measures and patients evaluated. This may be explained by two causes. First, real images were used; thus, even if their quality was visually assessed, there may be inhomogeneities and noise. Second, similarity measures were estimated from random voxel samples lying in the common spatial domain.

There is an important overall variability with no clear advantage for a given similarity measure. In LGE-LGE study, NC and MI metrics performed the best overall (Table 1 (top)). It can be noted that MS-S improves ACC and DO near when compared to MS, but it degrades NOM and RON. Amongst MI metrics, VWMI resulted with a worst RON. We have selected NMI because it seems to have a good overall behavior compared to MMI and NC. In cine-LGE study, it is observed that MI metrics have a better behavior than MS-S and NC but VWMI resulted with the worst RON. Both, MMI and NMI seem to be a good choice for cine-LGE registration. We have selected NMI.

3.3. Evaluation of US and cine/LGE registration

The starting simplex for slice misalignment correction was set to (10, 10, 0.1, 0.1) which corresponds to the step further along x_1 , x_2 , σ_1 and σ_2 parametric space, respectively. Slice misalignment correction was applied when needed after visual assessment. Output slice misalignment transformations were propagated to the dynamic IV surface. For LGE and cine registration, the regular step gradient descent optimization used a min step of 0.5 and max step of 2.5. The scale

Table 1

Similarity measure properties for (top) rigid LGE registration, and (bottom) cine and LGE registration (SAX views). The properties are reported as mean \pm standard deviation. Best values per column are in bold type. Arrows indicate if the indicator has to be maximized (\nearrow) or minimized (\searrow). ACRONYMS – ACC: accuracy, CR: capture range, DO: distinctiveness of optimum, MI: mutual information, MMI: Mattes MI, MS: mean square metric, MS-S: MS of local entropy images, NMI: normalized MI, NOM: average number of minima, RON: risk of nonconvergence, VWMI: Viola-Wells MI.

Metric	ACC(\searrow) (in mm)	DO(\nearrow) near	($\times 10^{-2}$) far	CR(\nearrow)	NOM(\searrow)	RON(\searrow) near	($\times 10^2$) far
MS	1.1 \pm 0.5	0.3 \pm 0.2	2.2 \pm 1.5	0.165	0.6 \pm 0.8	1.1 \pm 0.9	0.6 \pm 1
MS-S	1.0 \pm 0.5	0.6 \pm 0.1	1.4 \pm 0.9	0.165	4.6 \pm 2.0	13.2 \pm 5.8	7.0 \pm 5.0
NC	0.9 \pm 0.6	0.2 \pm 0.1	2.0 \pm 1.5	0.165	0.2 \pm 0.2	1.1 \pm 1.2	0.1 \pm 0.1
VWMI	0.9 \pm 0.5	0.6 \pm 0.04	3.2 \pm 2.3	0.165	0.5 \pm 0.4	4.7 \pm 3.4	0.6 \pm 0.6
MMI	0.9 \pm 0.7	0.4 \pm 0.1	2.9 \pm 2.0	0.165	0.2 \pm 0.2	1.3 \pm 1.3	0.1 \pm 0.1
NMI	0.9 \pm 0.6	0.4 \pm 0.1	3.6 \pm 2.4	0.165	0.2 \pm 0.1	1.4 \pm 1.1	0.1 \pm 0.1
MS-S	1.7 \pm 1.0	0.9 \pm 0.4	1.4 \pm 1.1	0.165	4.7 \pm 3.9	12.5 \pm 17	36.8 \pm 23
NC	1.9 \pm 0.9	0.6 \pm 0.1	1.9 \pm 1.1	0.165	2.5 \pm 1.8	7.2 \pm 7.7	25.9 \pm 33
VWMI	1.3 \pm 1.2	1.7 \pm 0.2	2.7 \pm 1.9	0.165	3.2 \pm 1.5	33.4 \pm 28	21.4 \pm 24
MMI	2.2 \pm 1.9	0.9 \pm 0.7	2.7 \pm 1.4	0.165	1.7 \pm 0.8	5.6 \pm 3.9	5.9 \pm 1.9
NMI	1.6 \pm 1.3	1.3 \pm 1.0	2.7 \pm 1.4	0.165	0.8 \pm 0.2	7.1 \pm 6.5	7.6 \pm 1.7

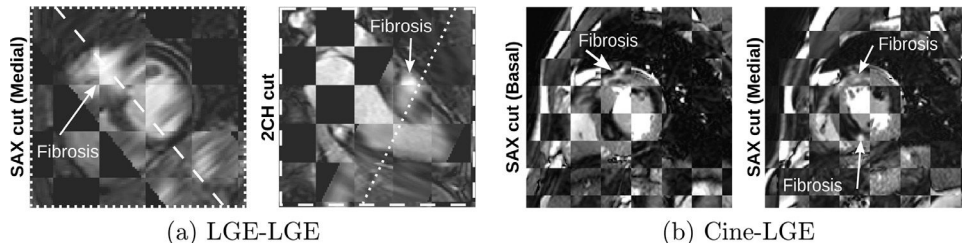


Fig. 5. Checkerboard of images used for the evaluation of similarity measures for the rigid registration of (a) LGE-SAX and LGE-2CH and (b) cine-SAX and LGE-SAX. LGE images were acquired using the IR technique.

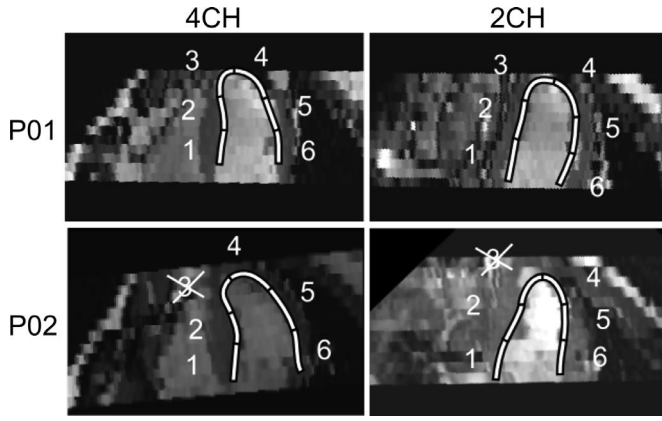


Fig. 6. Visual assessment of the combined registration of US-4CH and US-2CH to cine-SAX. The matching of regions in longitudinal LV contours (1, 2, 3, 4, 5, 6) with the myocardial wall from cine-SAX was assessed. Each region results from regional STE analysis. P01, P02 stand for patients 01 and 02, respectively.

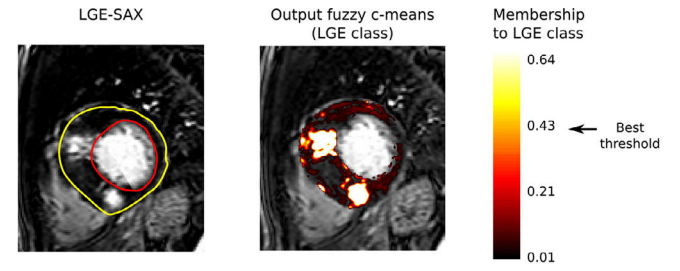
factor between rotations (in radians) and translations (in mm) was set to 10^5 . Both misalignment correction and the rigid registration were implemented using ITK (Johnson et al., 2013). LV contours from US were superimposed to both cine-SAX and LGE after registration.

Given the lack of gold standard, the alignment of US and cine-SAX was assessed visually by a cardiologist at peak-R (end-diastole), for acquisitions from 10 patients selected randomly. The LV contours from US-2CH and US-4CH were superimposed to cine-SAX using output US planes (Fig. 6). Each segment was rated as exploitable or non-exploitable (1 or 0) according to its alignment with cardiac structures in cine-SAX. The percentage of exploitable segments was used as a performance indicator. From a total of 120 segments (10 patients, 2 US views, 6 segments per view), 105 segments (87.5%) were successfully aligned. All non-aligned segments were located in the apical region. This is explained by the lack of detailed information in this region in both US and cine-SAX. The alignment of LV contours from US and multiview LGE was also visually assessed. The LV contours from US (2CH and 4CH) matching the acquisition time of LGE were superimposed to LGE-4CH and LGE-2CH (Fig. 8(top)). From 28 patients enrolled (330 segments in total), 306 segments (92.7%) were successfully aligned.

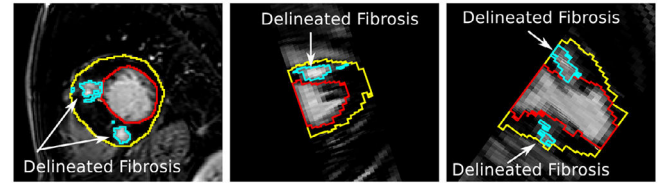
3.4. HCM characterization: strain modification and the presence of fibrosis

The fusion of US and LGE images provides insights about the abilities of STE analysis to characterize myocardial structure, especially for premature HCM when structural changes in myocardial tissue could be reversed. Previous studies have reported that regional myocardial strain and wall-thickening are affected by regional myocardial fibrosis in patients with HCM (Popović et al., 2008). However, the relationship between US-strain and fibrosis has not been clarified. Saito et al. (2012) reported a bulleye analysis of US-strain and tissue state from LGE but they did not consider the underlying mismatch between US and LGE (i.e. they lack of precise registration of these modalities). The proposed registration of US and LGE overcomes this problem.

We sought to associate the presence of fibrosis with regional peak-strain and peak-delay indicators aiming to study their abilities to predict the presence of fibrosis. Peak-strain was defined as the minimum value of the strain curve, while peak-delay was defined as the time delay of peak-strain from the beginning of QRS. Longitudinal strain curves from 2D TTE apical 4CH and 2CH views were used (Echo PAC BT12, GE Healthcare, Horten, Norway). Echocardiography readers were blinded to MRI results and did not have any clinical data when reading US files. Longitudinal strain was privileged because it is the



(a) LGE-SAX with inner and outer myocardial contours (left) and resulting membership to LGE-class (right)



(b) Extent of myocardial fibrosis after LGE class binarization using the best threshold shown in (a)(right)

Fig. 7. Extent of myocardial fibrosis computed from the LGE-SAX image of patient 01 using the method of Kachenoura et al. (2008) and the automatic threshold computation described in Baron et al. (2013).

component whose measurement is the most reproducible and robust. All LV segments correctly aligned with multiview LGE were used (306 in total).

The fuzzy c-means method of Kachenoura et al. (2008) was used to compute the average myocardial fibrosis extent per patient, expressed as a percentage of the myocardial volume. Required inner and outer contours of LV myocardium were manually delineated by a cardiologist. Fibrosis was delineated for each slice in LGE-SAX in two steps. In the first step, a fuzzy c-means procedure computed the membership of those voxels in the myocardium and blood pool to two classes: late gadolinium-enhanced class (LGE-class, see Fig. 7a) and non-enhanced class. In the second step, LGE-class membership of myocardial voxels was used to compute fibrosis extension by thresholding. The threshold providing the most stable output was used, as described in Baron et al. (2013). Both output slice misalignment transformations and the resulting rigid LGE-to-cine transformation were applied to resulting fibrosis segmentation. An instance of fibrosis delineation is presented in Fig. 7b. It can be noted that the extent of fibrosis was well-delineated in those regions with a high density of enhanced voxels. The validation of fibrosis segmentation was visually performed by a clinician. The HCM population under study resulted with an average of 10.5% of the myocardial volume affected by fibrosis (values between 0.6% and 43.5%, with a standard deviation of 11.7%). This finding is in agreement with clinical studies in Saito et al. (2012); Popović et al. (2008).

Fig. 8 presents an instance of US and LGE registration with associated regional strain curves and myocardial fibrosis. Myocardial fibrosis appears at basal-septal and mid-septal regions of US-4CH, and basal-ant, mid-ant and mid-inf regions of US-2CH. It can be noted an evident alteration of regional peak-strains in Fig. 8 for those regions with fibrosis. Two sets of US regions were then constructed in order to evaluate the abilities of regional strain indicators in localizing fibrosis: (i) US regions without fibrosis (235 segments, 76.79%) and (ii) US regions with fibrosis (71 segments, 23.20%). Boxplots depicting (i) peak-strain and (ii) peak-delay for these populations are presented in Fig. 9(left). The Mann-Whitney test ($\alpha=0.01$) rejected the null hypothesis of the two populations having the same mean ($p < 0.01$). Then, we conclude that the expected values of these indicators are different for the two populations. Therefore, the modification of regional peak-strain means that low regional longitudinal contraction

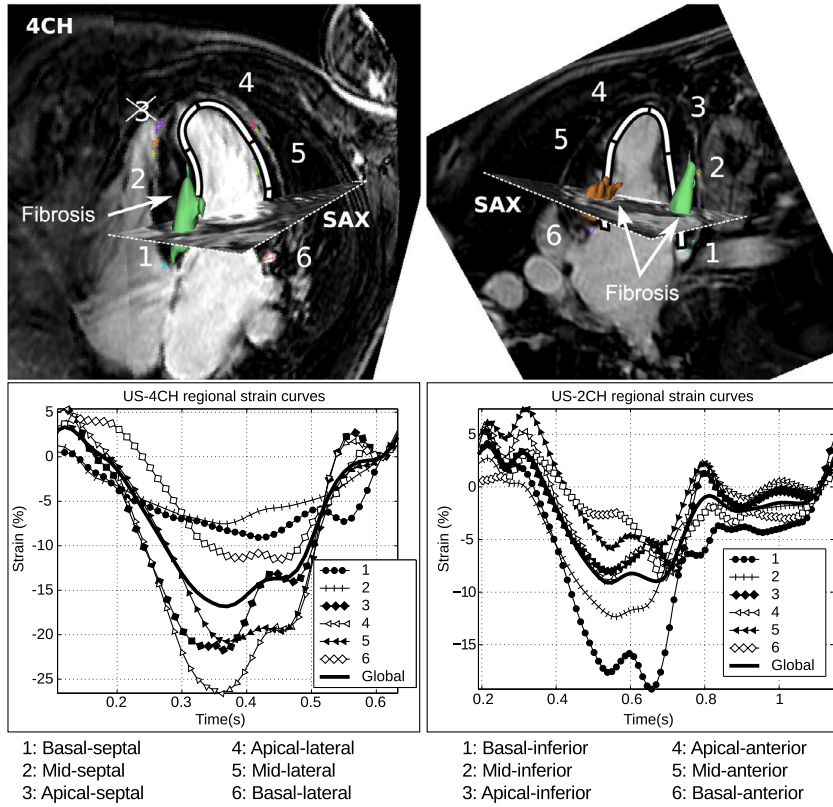


Fig. 8. Association of regional strain and fibrosis. (Top) LV contours superimposed to multiview LGE after registration. Regions with fibrosis resulted from the fuzzy c-means method (colored surfaces). (Bottom) Regional strain curves from US-4CH (left) and US-2CH (right).

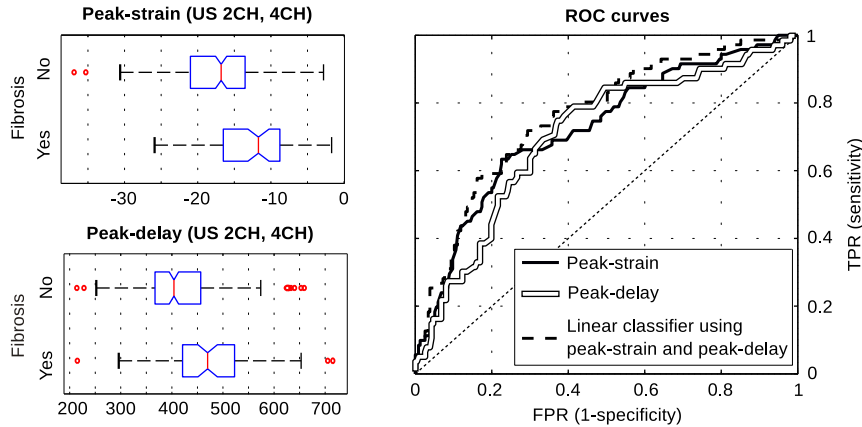


Fig. 9. Indicators from HCM population. Boxplots of peak-strain (top-left) and peak-delay (bottom-left), each for regions with/without fibrosis (box: 25 to 75 percentile, whiskers: approximately ± 2.7 sigma, circles: outliers). (Right) ROC curves for the strain indicators and for a linear classifier using them.

is an indicator of fibrosis. In fact, the magnitude of peak-strain decreases with the presence of fibrosis. On the other hand, a high peak-delay is also related to the presence of fibrosis.

Although the Mann-Whitney test proves the expected value of peak-strain and peak-delay varies between regions with/without fibrosis, their distribution overlaps (Fig. 9, left). To elucidate the strength of these indicators to predict the presence of fibrosis, a ROC curve was plotted for three binary classifiers: one for each indicator and another for a linear classifier using both indicators (Fig. 9, right). The area under the curves, computed using the trapezoidal integration rule, was 0.7237, 0.7001 and 0.7609 for peak-strain, peak-delay and the linear classifier, respectively. Although significant, these results suggest that other parameters may alter strain indicators

including diffuse fibrosis, age and loading condition (volemia, blood pressure). In fact, ROC curves show that strain indicators are more sensible than specific.

4. Conclusions and perspectives

In this paper, we proposed a registration procedure to integrate cardiac US and LGE MRI. The procedure registers both multiview 2D US and LGE to cine MRI.

One contribution of this work concerns the quantitative analysis of intensity-based similarity measures to correct for slice misalignment and register cine and LGE MRI. This analysis proved to be useful to describe the performance of classic monomodal and

multimodal similarity measures. Nevertheless, high variability of performance indicators prevented to have a clear advantage for a given similarity measure. We showed that mutual information seems the best for slice misalignment correction in LGE and for the registration of multiview LGE and cine. This study may be enhanced by including more images to evaluate inter-patient variability. It can also be extended to correct other contrast-enhanced acquisitions such as dynamic contrast-enhanced MRI or CT.

Concerning dynamic US and cine MRI registration, we proposed to handle the temporal resolution difference and the variation in cardiac dynamics between these modalities by the use of an adapted dynamic time warping procedure. This procedure computes a spatio-temporal similarity measurement between dynamic geometries of the left ventricle. The results proved a good match between LV contours from US and underlying cardiac structures in cine and LGE MRI.

This work contributes to the characterization of hypertrophic cardiomyopathy. Indeed, the fusion of multiview US and LGE enhanced the knowledge of heart multiphysics in the context of HCM disease. Particularly, it enabled to study the potential contribution of longitudinal US-strain to detect the presence of fibrosis. Results from 28 patients proved that peak-strain and peak-delay indicators change with the presence of fibrosis. Further ROC analysis proved that these indicators are more sensitive than specific.

Future work will focus on integrating 3D ultrasound images to enhance US description with regards to fibrosis. In fact, 3D US images enable the study of the incidence of fibrous tissue in local/regional surface strain measurements. In this context, the use of T1-mapping sequences from cardiac MRI examination will be investigated to add diffuse fibrosis into the strain/fibrosis analysis.

Acknowledgments

This work was supported in part by French National Research Agency (ANR) through project Labex “Computer Assisted Medical Interventions” (Labex CAMI: ANR-11-LABX-0004-01). It was conducted in part in the experimental platform TherA-Image (Rennes, France) supported by Europe FEDER, in collaboration with the Center of Clinical Research and Technological Innovation of Rennes (CIC-IT 804).

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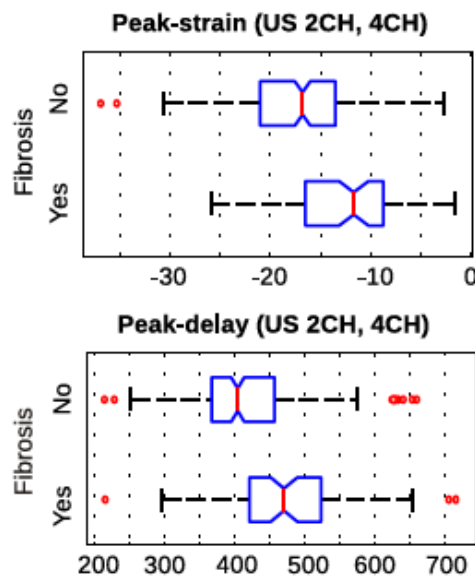
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3.2. Intérêt de l'échocardiographie d'effort

3.2.1. Comme outil de diagnostique : Impact du type de CMH

Le 2D strain semble être un outil intéressant afin de détecter la fibrose myocardique. En effet, les segments avec rehaussement tardif sont associés à une altération de la valeur du pic de 2D strain mais également à une contraction retardée.

Néanmoins, nous avons constaté dans le travail précédent qu'il existait un chevauchement important des valeurs de pic de strain ainsi que des délais de contraction entre les segments sains et avec fibrose myocardique.



Nous avons essayé de mieux comprendre l'altération du strain longitudinal au moyen d'une étude collaborative avec le CHU de Bordeaux. Nous avons donc comparé différents types morphologiques de CMH. Afin de sensibiliser les données échocardiographiques nous avons également intégré des données d'échocardiographie d'effort et notamment le caractère obstructif des CMH à l'effort. Dans ce travail nous n'avons pas utilisé l'évaluation du 2D strain à l'effort.

Apport du candidat dans ce travail

Mise en commun de ma base de données prospective des CMH. Près de la moitié des patients sont issus de la base de données rennaise réalisée dans le cadre de ma thèse. Relecture et correction du manuscrit.

RESUME

Objectifs : L'analyse du strain longitudinal permet une détection précoce de la dysfonction systolique ventriculaire gauche (VG) chez les patients avec fraction d'éjection préservée. Dans les cardiomyopathies hypertrophiques (CMH) on observe une altération des déformations myocardiques longitudinales régionales et globales. Les anomalies de strain VG régional sont en partie liées au degré d'hypertrophie. Cette étude visait à décrire le strain global longitudinal (GLS) chez des patients présentant différents types morphologiques de CMH, classés en fonction de la classification de Maron.

Méthodes et résultats : Des analyses échocardiographiques complètes intégrant l'analyse du GLS ont été réalisées chez des sujets atteints de CMH, inclus de manière consécutive dans 2 centres français de compétence dans la CMH. 271 patients (âge moyen 49 ± 16 ans; 71% d'hommes) ont été évalués. Dans cette population, le type II de Maron était le type de CMH le plus fréquent (47%). Le type III présentait une masse VG et une épaisseur pariétale plus élevée, plus d'obstruction au repos, des valeurs de GLS plus basses (-15.3 ± 3.9 %, $P = 0.016$), un ratio E/E' plus élevé (13.4 ± 6.7 , $P < 0.001$), et plus fréquemment une réponse inadaptée de la pression artérielle à l'effort (30%, $P = 0.04$) en comparaison avec les autres types de CMH. La masse VG indexée était la variable qui était le plus corrélée avec le GLS ($r = 0.49$, $P < 0.01$), alors que le GLS ne corrélait pas de manière significative avec l'obstruction intra VG.

Conclusion : Cette étude a démontré que le type III de la classification de Maron était le type de CMH avec le plus faible GLS, en partie en lien avec une masse VG indexée plus élevée, des pressions de remplissage plus élevées et une réponse inadaptée de la pression artérielle à l'effort plus fréquente en comparaison avec les autres types de CMH.

Clinical and imaging description of the Maron subtypes of hypertrophic cardiomyopathy

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Received: 24 April 2014 / Accepted: 1 September 2014
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Abstract Longitudinal strain analysis enables early detection of left ventricular (LV) contraction abnormalities in patients with preserved ejection fraction. Hypertrophic cardiomyopathy (HCM) is associated with low values of regional and global longitudinal myocardial deformations. In addition to contraction abnormalities, LV regional strain abnormalities are partially related to the degree of hypertrophy. This study sought to describe global longitudinal strain (GLS) in HCM patients as categorized using the Maron's classification. Complete echocardiography examinations, including GLS analysis, were performed in consecutive HCM patients followed up in two French HCM-clinics. A total of 271 patients (mean age 49 ± 16 yrs; 71 % male) were evaluated. In this population, the most frequently classified hypertrophy pattern was Type II (47 %), following the Maron's classification. Type III was characterized by a higher degree of LV hypertrophy in terms of mass and maximal wall thickness, and was more frequently obstructive at rest, with lower GLS values (-15.3 ± 3.9 %, $p = 0.016$), higher E/E' ratio (13.4 ± 6.7 , $p < 0.001$), and a more frequently inadequate blood pressure response to exercise (30 %, $p = 0.04$)

compared to other patterns. The variable that correlated best with GLS was LV mass index ($r = 0.49$, $p < 0.01$), while GLS did not significantly correlate with left ventricular outflow tract obstruction. This study demonstrated that the Type III HCM pattern presented with lower GLS, which was partially related to higher LV mass index, more elevated LV filling pressures, and a more frequently inadequate blood pressure response to exercise, in comparison with other patterns categorized using the Maron's classification.

Keywords Echocardiography · Hypertrophic cardiomyopathy · Myocardial strain · Speckle-tracking echocardiography

Abbreviations

GLS	Global longitudinal strain
HCM	Hypertrophic cardiomyopathy
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVOTO	Left ventricular outflow tract obstruction

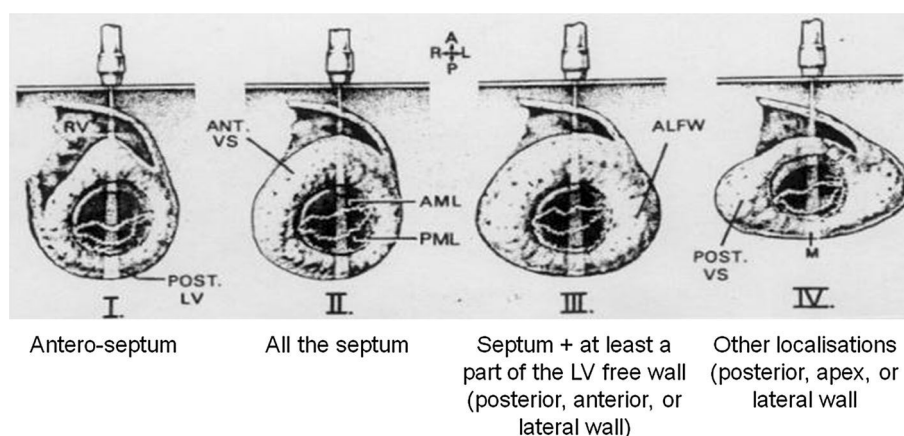
Introduction

Hypertrophic cardiomyopathy (HCM) presents with varying phenotypic and clinical expressions and is caused by a genetic disorder inducing myocardial disarray, hypertrophy, and energetic dysfunction of left ventricular (LV) myocytes, along with interstitial fibrosis. While LV outflow tract obstruction (LVOTO) occurring at rest [1, 2] or during exercise [3, 4] is related to poorer clinical outcomes in HCM patients, myocardial disease progression itself could

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Fig. 1 Example of a Bull's Eye plot of regional and global longitudinal strain in each Maron classification phenotype: **a** Type I: hypertrophy involving the basal septum; **b** Type II: hypertrophy involving the whole septum; **c** Type III: hypertrophy involving septum, anterior, and anterolateral walls; **d** Type IV: LV apical hypertrophy. According to Maron BJ. et al classification. Am J Cardiol 1981;48:418–28



also account for worsening symptoms. LV ejection fraction (EF) is, nevertheless, typically preserved in this disease. LV morphology, the repartition and degree of hypertrophy, as well as diastolic and systolic function are all equally relevant. Moreover, technological advances in echocardiography have emphasized the capacity of longitudinal strain analysis for early detection of LV contraction abnormalities in patients with a preserved EF [5]. HCM is associated with low values of regional and global longitudinal myocardial deformations [5]. Global longitudinal strain (GLS) analysis is known to be of higher prognostic value than LVEF in various cardiomyopathies [6–10]. Moreover, few studies suggest that it should be a good prognostic indicator in HCM patients [11]. In addition to contraction abnormalities, LV regional strain abnormalities are partially related to the degree of hypertrophy [12, 13]. Consequently, we sought to describe GLS in HCM patients according to the Maron's classification (Fig. 1), which outlines the categorization of LV hypertrophy [14].

Methods

This study prospectively evaluated HCM patients who were referred, between October 2009 and September 2012, to two regional French HCM Competence Centers, forming part of the University Cardiology Hospitals of Rennes and Bordeaux-Pessac. The patients were investigated at baseline using clinical parameters, two-dimensional (2D) echocardiography both at rest and during exercise to detect inducible LVOTO and evaluate functional tolerance, and cardiac MRI if possible.

The study inclusion criteria were as follows: (1) previous formal diagnosis of HCM based on morphological hypertrophy, genetic tests, or family history; (2) sinus rhythm; (3) ability to perform bicycle exercise testing.

Morphologic HCM diagnoses were based on a 2D echocardiographic detection of a hypertrophied, non-

dilated LV (wall thickness of at least 15 mm in adults, 13 mm when positive for HCM family history), in the absence of other cardiac or systemic diseases susceptible to producing a similar degree of hypertrophy [15].

Exclusion criteria were as follows: (1) poor ultrasound window quality; (2) contraindication to exercise testing according to standard clinical guidelines [including New York Heart Association (NYHA) functional Class IV or physical reasons] [16].

Medication was not interrupted prior to echocardiography. All patients were provided with comprehensive information regarding the study and data collection, and the Institutional Review board approved the study protocol.

Resting 2D echocardiography was conducted according to the combined ASE/EAE guidelines [17, 18] with ultrasound recordings obtained using a Vivid 9 (General Electric Medical System, Horten, Norway) by an experienced (Level three) operator [19]. Recordings in standardized views were acquired in 2D, pulsed, continuous, and color Doppler modalities, then stored for subsequent analysis, also including a 70 Hz rate acquisition in the apical views for strain analysis by speckle-tracking. Pulsed tissue Doppler imaging analysis was carried out in the apical 4-chamber view at the lateral and septal sides of the mitral annulus and at the lateral free side of the right ventricle. LVOT was scanned by means of continuous wave Doppler to measure maximal outflow velocity.

Exercise echocardiography was conducted following EAE guidelines [16]. Exercise consisted of a bicycle exertion test with the patient in a semi-supine position (50°) with a slight left lateral tilt so as to enable simultaneous transthoracic echocardiography. The workload was initially set at 25 W, then increased by 25 W every 2 min, up to the maximum tolerated effort. At each stage from rest to recovery, conventional recordings were acquired in 2D views and continuous and color Doppler modalities, then stored for offline analysis. Systolic and diastolic blood pressures, along with the ECG, were recorded from rest to

recovery at each stage. Blood pressure was measured by means of a cuff sphygmomanometer. Inadequate blood pressure response to exercise was defined as an increase in systolic blood pressure <25 mmHg or a drop in systolic blood pressure at peak ≥ 15 mmHg.

An independent observer, blinded to patient history, analyzed all cases retrospectively, applying standard measurements according to EAE/ASE guidelines, and using the quantitation package provided with the echograph machine. Localization of hypertrophy was established in accordance with the Maron's classification as follows: [14, 20] Type I pattern involving only the antero-septum, Type II involving the whole septum wall, Type III involving the septum and, at least in part, the LV free wall, and Type IV involving other localizations (posterior, apex, or lateral wall) (Fig. 1). Maximal end-diastolic wall thickness was measured in 2D. LV diameters and volumes, along with LVEF, were calculated from the apical two- and four-chamber views by applying Simpson's rule [17, 18]. Biplane maximal left atrial volume was calculated using the area-length method [17]. LV filling pressures were estimated from the ratio of mitral orifice E and septal and lateral annular E' peak velocities (the E/E' ratio). Systolic pulmonary artery pressure was calculated [21]. Mitral regurgitation, if present, was graded (0–3) following the PISA method. For the right ventricle, systolic function was assessed using tissue Doppler imaging (peak S' at the lateral free wall), and tricuspid anterior–posterior systolic excursion by applying the M-mode. The length of the anterior mitral leaflet was measured based on the parasternal long-axis view during mid-diastole. Mitral annulus diameter was measured in the parasternal long axis view. Systolic anterior motion of the mitral valve was considered present only if complete. Outflow gradients were measured and automatically calculated from the flow velocities by means of the modified Bernoulli equation [22]. Outflow velocities were measured using continuous-wave Doppler during exercise, applying the same direction and angle as recorded at rest. Longitudinal LV deformation was measured using the 2D speckle-tracking echocardiographic method [23]. Following the positioning of three endocardial markers in an end-diastolic frame, the software automatically tracked the contour over subsequent frames. We were able to verify tracking adequacy in real-time, and make any necessary corrections by adjusting the region of interest or manually correcting the contour, to ensure optimal tracking. Longitudinal strain was assessed in apical views. Average longitudinal strains were calculated for the 17 segments in relation to the strain magnitude at aortic valve closure, and LV GLS value was obtained. Longitudinal systolic deformation was characterized as shortening, and by definition yields a negative value.

Cardiac magnetic resonance imaging was performed on all patients who presented with no standard contraindications, such as a non-MRI compatible pacemaker or implantable cardioverter defibrillator, other metal implants, claustrophobia, or severe renal failure. Imaging was conducted using 1.5 or 3.0 Tesla, Avanto machine (Siemens®), and CMR tools® for LV volume and mass quantification. Late gadolinium enhancements were analyzed qualitatively.

All statistical analyses were performed using SPSS (Version 17.0, SPSS Inc., Chicago, IL, USA), and the data was expressed as mean \pm SD. The unpaired Student's *t*-test, one-way analysis of variance, and ANOVA analyses were employed in order to compare normally-distributed data. Pearson's Chi-squared and Fisher's exact tests were performed to compare non-continuous variables expressed as proportions, and the Pearson correlation coefficient was also used. *P* values were two-sided, and a *p* value ≤ 0.05 was considered statistically significant.

Results

The study initially enrolled 316 HCM patients. Twelve patients with permanent atrial fibrillation were excluded from analysis, as were a further 23 due to poor acoustic windows, and 10 patients in NYHA Class IV grade. This resulted in a total of 271 patients included for echocardiographic analysis at rest and during exercise. Patients mean age was 48.8 ± 15.9 years, and 193 (71 %) were male.

In total, 11 % ($N = 30$) of patients presented with a Type I pattern, 47 % ($N = 127$) Type II, 35 % ($N = 94$) Type III, and 7 % ($N = 20$) Type IV. As shown in Table 1, the four hypertrophy patterns differed with respect to several baseline characteristics. While no significant difference was observed in terms of gender, Type I patients were found to be significantly older, whereas Type IV patients were younger than the other groups. HCM family history and sudden cardiac death were significantly more common in Type II (51 and 38 %, respectively) and, to a lower extent, in Type III than in Types I and IV. Patients with Type IV hypertrophy exhibited less dyspnea at exertion than the three other groups, and were less frequently undergoing medical treatment.

At rest echocardiography, as shown in Table 2, patients with a Type III classified pattern exhibited more frequently a maximal LV hypertrophy ≥ 30 mm (11 %), with significantly lower GLS values (-15.3 ± 3.9 % in Type III vs. -16.9 ± 3.6 % in Type I, -17.0 ± 3.3 % in Type II, and -17.3 ± 4.0 % in Type IV; $p = 0.016$), and significantly higher mean E/E' ratios than other groups, which indicated higher LV filling pressures.

Table 1 Baseline clinical characteristics of HCM patients according to Maron's morphologic classification

Variables	All (N = 271)	Type I (N = 30)	Type II (N = 127)	Type III (N = 94)	Type IV (N = 20)	<i>p</i> value
Male gender—no. (%)	193 (71)	20 (67)	93 (73)	63 (67)	17 (85)	0.36
Age (yrs)	48.8 ± 15.9	56.3 ± 12.9	47.9 ± 15.9	49.8 ± 16.4	38.8 ± 15.7	0.001
Weight (kg)	76.2 ± 14.8	79.5 ± 9.7	76.8 ± 14.8	74.9 ± 16.2	73.8 ± 14.6	0.40
Height (m)	169.9 ± 10.4	169.0 ± 11.4	169.4 ± 10.9	170.2 ± 9.4	172.4 ± 10.3	0.64
Body surface area (m ²)	1.9 ± 0.2	1.9 ± 0.1	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.65
Age of HCM discovery (yrs)	42.4 ± 18.2	52.3 ± 16.6	40.8 ± 17.6	42.7 ± 18.8	35.9 ± 16.2	0.006
Family history of HCM—no. (%)	115 (42)	7 (23)	65 (51)	37 (39)	6 (30)	0.017
Hypertension—no. (%)	68 (25)	11 (37)	28 (22)	27 (29)	2 (10)	0.12
Paroxysmal atrial fibrillation—no. (%)	34 (13)	3 (10)	14 (11)	15 (16)	2 (10)	0.67
Known coronary disease—no. (%)	5 (2)	0 (0)	4 (3)	1 (1)	0 (0)	0.49
History of embolism—no. (%)	22 (8)	4 (13)	6 (5)	11 (12)	1 (5)	0.18
Systolic blood pressure (mmHg)	133 ± 20	137 ± 18	132 ± 21	134 ± 20	129 ± 18	0.52
Diastolic blood pressure (mmHg)	76 ± 12	80 ± 9	75 ± 12	76 ± 14	76 ± 9	0.29
Heart rate (bpm)	65.7 ± 12.3	63.1 ± 10.7	66.4 ± 11.7	64.8 ± 13.4	69.5 ± 12.9	0.25
Chest pain—no. (%)	28 (10)	1 (3)	18 (14)	8 (9)	1 (5)	0.21
Dyspnea at exertion	133 (49)	17 (57)	63 (50)	50 (53)	3 (15)	0.013
NYHA class						
I—no. (%)	138 (51)	13 (43)	64 (50)	44 (47)	17 (85)	0.05
II—no. (%)	119 (44)	17 (57)	57 (45)	43 (46)	2 (10)	
III—no. (%)	14 (5)	0 (0)	6 (5)	7 (7)	1 (5)	
Betablocker—no. (%)	190 (70)	22 (73)	85 (67)	74 (79)	9 (45)	0.017
Calcium antagonist—no. (%)	35 (13)	3 (10)	19 (15)	11 (12)	2 (10)	0.81
CEI/ARAI—no. (%)	59 (22)	13 (43)	25 (20)	20 (21)	1 (5)	0.008
Implantable cardiac defibrillator—no (%)	34 (13)	2 (7)	17 (13)	15 (16)	0 (0)	0.18
Syncope/lipothymia—no. (%)	54 (20)	4 (13)	30 (24)	17 (18)	3 (15)	0.50
Abnormal blood pressure response to exercise—no. (%)	57 (21)	5 (17)	21 (17)	28 (30)	3 (15)	0.044
Non-sustained ventricular tachycardia—no. (%)	35 (13)	2 (7)	19 (15)	13 (14)	1 (5)	0.44
LV hypertrophy ≥30 mm—no. (%)	19 (7)	0 (0)	8 (6)	10 (11)	1 (5)	0.22
Family history of sudden cardiac death—no. (%)	82 (30)	4 (13)	48 (38)	27 (29)	3 (15)	0.02
NT-pro BNP (pg/ml)	875 ± 1,392	698 ± 1,032	759 ± 979	1,063 ± 1,816	612 ± 547	0.74

HCM hypertrophic cardiomyopathy, CEI/ARAI conversion enzyme inhibitor/angiotensin II receptor antagonist, LV left ventricular, BNP brain natriuretic peptid

At exercise echocardiography (Table 3), Type III patients exhibited significantly lower exercise tolerance in watts ($p = 0.002$), and were more likely to present with abnormal blood pressure responses to exercise (30 % of cases, $p = 0.044$).

In Table 4, LV systolic function echocardiographic parameters at rest and peak exercise were compared across Types I, II, and III of the Maron's classification, based on presence or absence of LVOTO. No differences were observed in terms of LVEF values, yet GLS was particularly impaired in Type III patients with LVOTO.

The strain data provided in Fig. 2 shows an example of GLS in each phenotype, as categorized by the Maron's classification.

Cardiac magnetic resonance imaging characteristics are provided in Table 5. As expected, patients with Type III pattern displayed higher indexed LV mass than those with other hypertrophy patterns. No significant differences were recorded in terms of LVEF across the four groups. Types I and IV HCM patterns tended to exhibit less frequently late gadolinium enhancements than the others.

Table 6 displays the Pearson correlations between GLS and the other primary variables. Indexed LV mass was

Table 2 Resting echocardiographic characteristics

Variables	All (N = 271)	Type I (N = 30)	Type II (N = 127)	Type III (N = 94)	Type IV (N = 20)	p value
Maximal wall thickness (mm)	20.6 ± 5.0	18.5 ± 3.6	20.7 ± 4.7	21.4 ± 5.7	19.2 ± 3.8	0.23
Maximal wall thickness ≥30 mm—no. (%)	19 (7)	0 (0)	8 (6)	10 (11)	1 (5)	0.22
Maximal septal thickness (mm)	18.9 ± 5.3	18.5 ± 3.6	20.7 ± 4.7	21.4 ± 5.7	19.2 ± 3.8	<0.001
LV end-diastolic volume (ml)	81.5 ± 24.5	82.4 ± 20.9	81.4 ± 23.3	79.3 ± 25.9	92.0 ± 28.6	0.21
LV end-systolic volume (ml)	26.2 ± 11.8	25.6 ± 10.5	26.0 ± 11.3	26.0 ± 12.2	29.0 ± 15.0	0.74
LV ejection fraction (Simpson) (%)	68.2 ± 8.1	69.1 ± 8.7	68.4 ± 7.7	67.5 ± 8.4	68.9 ± 8.4	0.75
Global longitudinal strain (%)	−16.4 ± 3.7	−16.9 ± 3.6	−17.0 ± 3.3	−15.3 ± 3.9	−17.3 ± 4.0	0.016
Indexed biplane LA volume (ml/m ²)	31.9 ± 16.0	30.0 ± 14.4	33.4 ± 16.0	32.0 ± 17.1	24.3 ± 11.3	0.11
Peak E mitral wave (cm)	75.4 ± 21.2	77.9 ± 25.9	76.2 ± 21.0	73.8 ± 18.8	74.1 ± 25.8	0.75
Peak A mitral wave (cm)	66.5 ± 23.8	76.9 ± 25.9	64.6 ± 23.2	68.6 ± 23.9	53.4 ± 15.8	0.004
Mitral E/A	1.3 ± 0.7	1.1 ± 0.6	1.4 ± 0.9	1.2 ± 0.5	1.5 ± 0.9	0.063
Deceleration time E mitral wave (ms)	234 ± 75	247 ± 80	228 ± 65	243 ± 88	202 ± 53	0.087
Septal S' (cm/s)	7.7 ± 2.1	8.6 ± 3.3	7.7 ± 1.9	7.2 ± 1.7	8.7 ± 2.2	0.003
Septal E' (cm/s)	6.3 ± 2.5	6.6 ± 2.4	6.4 ± 2.1	5.6 ± 2.5	8.7 ± 3.3	<0.001
Septal A' (cm/s)	8.0 ± 2.5	9.0 ± 2.7	8.0 ± 2.7	7.6 ± 2.4	8.1 ± 2.1	0.003
Lateral S' (cm/s)	8.6 ± 2.7	9.1 ± 2.9	8.6 ± 2.6	8.0 ± 2.7	10.2 ± 2.7	0.009
Lateral E' (cm/s)	9.4 ± 3.8	9.6 ± 4.1	9.8 ± 3.7	8.4 ± 3.6	11.2 ± 4.1	0.006
Lateral A' (cm/s)	8.6 ± 3.3	10.0 ± 2.9	9.0 ± 3.4	7.8 ± 3.2	7.9 ± 2.3	0.003
Septal E/E'	13.6 ± 6.8	13.2 ± 6.0	12.8 ± 5.6	15.7 ± 8.1	9.5 ± 4.5	0.001
Lateral E/E'	9.4 ± 5.0	9.3 ± 4.1	8.9 ± 4.5	10.7 ± 5.7	7.3 ± 4.3	0.016
Mean E/E'	11.5 ± 5.5	11.3 ± 4.9	10.8 ± 4.5	13.4 ± 6.7	8.4 ± 4.3	<0.001
LVOT gradient ≥30 mmHg at rest—no. (%)	65 (24)	6 (20)	32 (25)	27 (29)	0 (0)	0.049
Maximal LVOT gradient (mmHg)	21.7 ± 28.2	18.7 ± 21.0	24.0 ± 32.7	22.8 ± 25.7	6.1 ± 2.6	0.059
Systolic anterior motion of the mitral valve—no. (%)	57 (21)	6 (20)	28 (22)	23 (94)	0 (0)	0.11
Mitral regurgitation grade (median)	0.0	0.0	0.0	0.0	0.0	0.14
Systolic pulmonary artery pressure (mmHg)	27.5 ± 9.1	27.4 ± 9.4	27.3 ± 9.9	29.3 ± 7.4	21.5 ± 6.4	0.051
Right ventricular S' (cm/s)	11.6 ± 4.1	10.3 ± 3.3	12.5 ± 3.8	10.9 ± 4.0	11.5 ± 5.6	0.013
Tricuspid antero-posterior systolic excursion (mm)	22.2 ± 4.5	22.3 ± 5.6	21.8 ± 4.6	22.3 ± 4.3	23.4 ± 3.5	0.59

found to correlate the best with GLS ($r = -0.49$, $p < 0.01$). It was interesting to observe that no significant correlation existed between GLS and peak LVOT gradient.

Discussion

This prospective descriptive clinical and imaging cohort study, conducted in a west-European population of HCM patients, confirmed the previous observations of Maron BJ et al. [14].

In line with our data, these authors found that Type III patients were more symptomatic, exhibiting significantly higher LVOTO at rest, and that Type I patients were older, and Type IV patients younger than those of other patterns. Yet our study has produced a more extensive characterization of Type III as a more severe phenotype, based on

higher LV mass index on MRI, higher LV filling pressure elevation (E/E'), more impaired GLS, which is mostly related to LV mass but not to LVOTO, lower exercise tolerance, and a more frequently abnormal blood pressure response to exercise, in comparison with the other patterns. The original Maron's classification was established three decades ago, and was based on an analysis of 125 American HCM patients with HCM family history, reporting 21 % of patients with Type I, 26 % Type II, 45 % Type III, and 18 % Type IV [14]. In our study involving 271 French HCM patients, we found that 11 % of patients exhibited the Type I pattern, 47 % Type II, 35 % Type III, and 7 % Type IV. These results likely differ from those cited above as they are based on a European population. Our findings may also been influenced by the efforts now made, three decades after the first study, to better differentiate sarcomeric HCM presentation from other causes of LV hypertrophy,

Table 3 Exercise echocardiographic characteristics

Variables	All (N = 271)	Type I (N = 30)	Type II (N = 127)	Type III (N = 94)	Type IV (N = 20)	<i>p</i> value
Under betablocker or calcic inhibitor—no. (%)	180 (66)	20 (67)	81 (64)	71 (76)	8 (40)	0.17
Maximal exercise tolerance (Watts)	120 ± 49	112 ± 52	128 ± 47	108 ± 46	143 ± 56	0.002
Theoretical maximal heart rate (%)	70 ± 14	70 ± 16	73 ± 15	66 ± 10	67 ± 11	0.005
Peak systolic blood pressure (mmHg)	168 ± 32	174 ± 26	171 ± 31	161 ± 34	165 ± 31	0.10
Peak diastolic blood pressure (mmHg)	81 ± 20	86 ± 11	81 ± 19	80 ± 22	79 ± 18	0.58
Peak heart rate (bpm)	118 ± 22	112 ± 21	124 ± 24	111 ± 18	117 ± 11	<0.001
LV end-diastolic volume (ml)	77.7 ± 25.3	78.6 ± 24.5	73.6 ± 22.9	81.0 ± 27.3	84.9 ± 28.5	0.12
LV end-systolic volume (ml)	23.4 ± 12.1	22.3 ± 10.5	22.7 ± 11.3	24.4 ± 13.7	23.8 ± 11.4	0.75
Peak LV ejection fraction (Simpson) (%)	70.5 ± 9.1	73.0 ± 8.2	69.8 ± 8.1	70.2 ± 10.3	72.8 ± 10.0	0.28
Mitral regurgitation grade (median)	0.0	0.0	0.0	0.0	0.0	0.21
Peak LVOT gradient ≥30 mmHg—no. (%)	101 (37)	12 (40)	51 (41)	37 (40)	1 (5)	0.019
Peak LVOT gradient (mmHg)	34.6 ± 39.7	33.4 ± 38.4	37.0 ± 41.9	36.3 ± 40.3	12.9 ± 7.4	0.083
Recovery LVOT gradient (mmHg)	63.5 ± 55.3	72.1 ± 53.8	56.6 ± 52.1	78.0 ± 60.8	26.2 ± 22.2	0.077
Ventricular tachycardia—no. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Abnormal blood pressure response to exercise—no. (%)	57 (21)	5 (19)	21 (17)	28 (30)	3 (18)	0.044

NA not applicable

Table 4 Systolic functional characterisation according to Maron's classification and to the presence/absence of LVOTO

	Type I (N = 30)	Type II (N = 127)	Type III (N = 94)	<i>p</i>
Rest LVEF (%)				
Obstructive	72.8 ± 7.3	69.3 ± 7.5	68.7 ± 7.9	0.25
Non obstructive	66.5 ± 8.8	67.8 ± 7.8	66.7 ± 8.7	0.71
GLS (%)				
Obstructive	−17.0 ± 4.0	−17.3 ± 3.5	−14.7 ± 3.6	0.006
Non obstructive	−16.8 ± 3.3	−16.7 ± 3.2	−15.9 ± 4.2	0.51
Peak LVEF (%)				
Obstructive	73.9 ± 5.7	72.0 ± 6.8	72.0 ± 8.3	0.76
Non obstructive	72.5 ± 9.5	68.4 ± 8.6	69.0 ± 11.3	0.32

such as hypertensive hypertrophy, septal bulge related to elderly, familial amyloidosis, or Anderson-Fabry disease, particularly with the routine use of genetic testing for familial screening. Furthermore, technological advances in transducers and echo-machines achieved in the last three decades now enable better visualization and detection of myocardial wall borders in each incidence, as well as a better analysis of the lateral, anterior, and apical walls (with the possibility of employing contrast LV opacification in difficult cases). Our analysis concerning this morphological picture was limited by the exclusion of 10 patients classified as NYHA Class IV, as well as those in permanent atrial fibrillation who could exhibit more severe profiles potentially related to Type III. Generally speaking, however, end-stage heart failure is mostly associated with parietal wall thinning and LV systolic dysfunction evolution. Our study completed the description of Maron

classification with the benefit of new advances in imaging, producing a more extensive characterization of the Type III of Maron's morphologic classification as a more severe phenotype than other groups, based on a higher LV mass index detected on cardiac magnetic resonance imaging, higher LV filling pressure elevation, more impaired GLS, which is mostly related to LV mass but not to LVOTO, lower exercise tolerance, and a more frequently abnormal blood pressure response to exercise (30 % of cases).

We have previously demonstrated that LV longitudinal strain analysis using speckle-tracking technology is a crucial tool for the demonstration and quantification of LV systolic impairment, while LVEF remains preserved in HCM patients, and that the disease severity in terms of systolic impairment cannot be adequately estimated based on LVEF [5]. In their recent study, Inoue K et al. [23] also demonstrated the value of studying LV morphology and

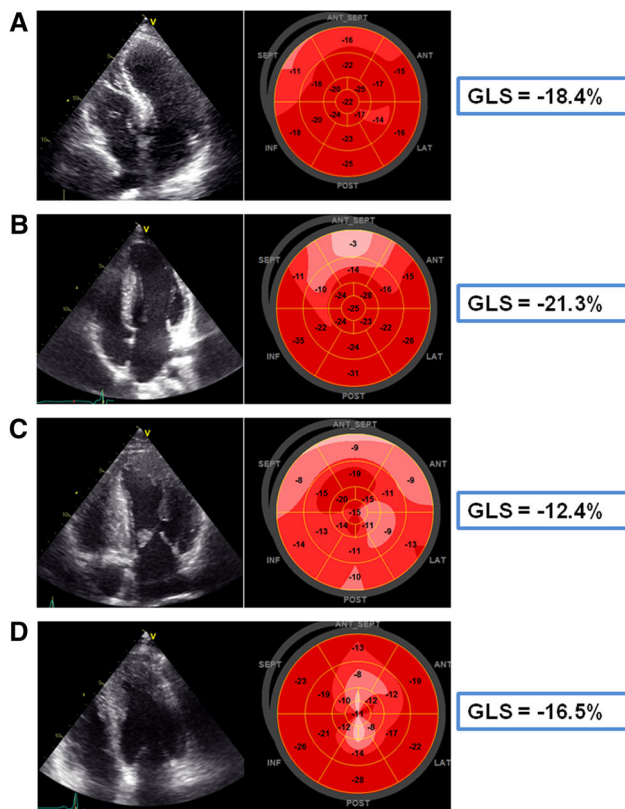


Fig. 2 Example of global and regional strain analysis in each Maron's classification subtype. Bull eye presentation. **A** type I, **B** type II, **C** type III, and **D** type IV. Global longitudinal strain is particularly decreased in type III (C)

septal longitudinal strain in HCM, with an inverse relation to the degree of septal curvature indicating a possible link between LV wall configuration and regional myocardial function. These authors observed a significant link between regional septal thickness and strain, as has also been demonstrated previously by Yang et al. [12]. Using the vector velocity imaging technique, Carasso et al. [13] have also reported evidence of differences in LV mechanics, yet at a regional level, in two HCM different patterns (septal vs. apical), proceeding to demonstrate their relation to regional thickness. Our study results were in line with these

Table 6 Relation between GLS and other variables in HCM

Variables	r	p value
Age (years)	0.08	0.23
LV mass index (g/m ²)	0.49	<0.01
LV end-diastolic volume (ml)	0.06	0.38
LV end-systolic volume (ml)	0.27	<0.01
LV EF (Simpson) (%)	-0.34	<0.01
Mean E/E'	0.20	0.78
Indexed biplane left atrial volume (ml/m ²)	0.22	<0.01
Maximal exercise tolerance (Watts)	-0.24	<0.01
Peak LVOT gradient (mmHg)	0.05	0.50

previous, and we have reinforced the hypothesis by taking a global approach integrating both LV hypertrophy categorization in HCM and GLS analysis. Furthermore, we have pointed the Type III of the Maron's classification as a poorer phenotype than the other LV hypertrophic categorized patterns. We have also confirmed the link between an LV global degree of hypertrophy and GLS. In addition, we did not observe any significant correlation between GLS and LVOT gradient at peak exercise. Finally, a pilot study conducted by Saito et al. underlined the prognostic value of reduced GLS in predicting poor outcomes in HCM patients, particularly in terms of heart failure progression [10]. Nevertheless, long-term follow-up studies are yet required in order to clearly assess the predictive value of GLS in HCM outcome, particularly regarding the Type III pattern. We did not analyze the circumferential and radial components of deformation, as these parameters are less accurate and less reproducible, particularly in a remodeled LV.

This was a descriptive study, outcomes data were not assessed here. However, GLS correlates with several already established markers (LV mass, LV filling pressures), reflects more intrinsèque myocyte function than these other markers, and allows earlier detection of LV systolic function abnormalities while EF is generally preserved in HCM. Moreover, it is readily available in most of

Table 5 Cardiac magnetic resonance imaging characteristics

Variables	All (N = 193)	Type I (N = 23)	Type II (N = 83)	Type III (N = 68)	Type IV (N = 19)	p value
LV end-diastolic volume (ml)	131.0 ± 35.5	121.0 ± 32.7	134.8 ± 34.5	129.7 ± 39.9	132.8 ± 24.6	0.39
LV end-systolic volume (ml)	40.9 ± 18.5	39.0 ± 18.4	42.8 ± 19.6	39.4 ± 18.5	41.2 ± 14.3	0.67
LV ejection fraction (%)	69.2 ± 9.0	68.0 ± 9.8	69.0 ± 8.9	69.8 ± 9.2	69.7 ± 7.9	0.84
Maximal wall thickness (mm)	20.0 ± 5.2	17.4 ± 3.7	19.6 ± 4.5	21.9 ± 6.1	18.4 ± 4.6	<0.001
LV mass (g)	185.3 ± 72.8	152.2 ± 51.3	176.0 ± 62.2	208.9 ± 88.7	182.1 ± 48.2	0.004
Indexed LV mass (g/m ²)	98 ± 35	80 ± 27	93 ± 30	111 ± 40	99 ± 23	0.001
Late gadolinium enhancement—no. (%)	130 (67)	11 (48)	59 (71)	50 (74)	10 (53)	0.056

the echocardiographs, with good reproducibility [5], and feasibility (92 % of the cases in the present study).

Conclusions

This descriptive cohort study more extensively demonstrates the Type III pattern of HCM as exhibiting a worse profile than other patterns, with a lower GLS. Reduced GLS correlated with several established prognostic markers: higher LV mass index, higher LV filling pressures, along with a more frequently abnormal blood pressure response during exercise echocardiography. Nevertheless, these results should be confirmed by studying outcomes.

Conflict of interest None.

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3.2. Intérêt de l'échocardiographie d'effort

3.2.1. Comme outil de diagnostique : Impact des conditions de charge

Nous avons démontré dans l'étude précédente que non seulement la fibrose, mais également la masse VG et les pressions de remplissage pouvaient expliquer l'altération des déformations myocardiques échographiques dans la CMH. Néanmoins, il avait dans de précédentes études sur l'animal été démontré que le 2D strain était post-charge dépendant ⁶⁰.

Afin de mieux caractériser l'effet des conditions de charge sur les paramètres de 2D strain dans le cadre du remodelage hypertrophique, nous avons inclus un autre modèle de remodelage hypertrophique pathologique, à savoir des patients présentant un rétrécissement aortique. Dans cette étude nous avons intégré les données de déformations myocardiques au cours d'un effort sous-maximal, volontairement limité à une cadence ventriculaire de 100-120 battements par minute. Ce choix d'un effort sous-maximal a été réalisé afin de pouvoir analyser le strain de manière fiable, tout en bénéficiant des modifications de contractilité et de charge induite par l'exercice.

Apport du candidat dans ce travail

Conception du projet. Inclusion de la majorité des sujets. Analyse de l'ensemble des données.
Rédaction du manuscrit.

RESUME

Objectifs : Il peut exister une altération de la fonction systolique ventriculaire gauche (VG) dans la cardiomyopathie hypertrophique (CMH) et le rétrécissement aortique (RAo) malgré une fraction d'éjection VG (FEVG) préservée. L'objectif de cette étude était de déterminer l'effet des conditions de post-charge et du degré d'hypertrophie VG sur les déformations myocardiques au repos et à l'effort.

Méthodes et résultats : Des patients avec un RAo modéré à sévère (surface aortique $\leq 1.5\text{cm}^2$) et des patients avec une CMH, en rythme sinusal, ont été étudiés prospectivement en échocardiographie de repos et au cours d'un exercice sous-maximal. Les déformations myocardiques ont été étudiées en utilisant le 2D strain. Les critères d'exclusion étaient : altération de la FEVG ($<50\%$), coronaropathie, obstruction intra-VG au repos $>30\text{mmHg}$, épaisseur pariétale $\geq 30\text{mm}$ et NYHA >2 . Cinquante patients (25 Rao et 25 CMH) ont été sélectionnés et appariés en fonction de l'âge, du sexe, de la pression artérielle de repos et d'effort, du degré d'hypertrophie pariétale (défini par l'épaisseur pariétale maximale) et de la FEVG.

Le strain global longitudinal moyen des RAo était de $-14.9 \pm 4.7\%$ vs. $-16.1 \pm 3.9\%$ dans les CMH ($P=0.30$). A l'effort (fréquence cardiaque moyenne 110 ± 10 bpm), le GLS moyen des RAo était de $-13.9 \pm 4.2\%$ vs. $-18.1 \pm 5.4\%$ dans les CMH ($P=0.004$). Le GLS diminuait chez les patients avec RAo mais augmentait dans les CMH (delta GLS $0.9 \pm 3.1\%$ et $-1.9 \pm 3.2\%$ respectivement, $P=0.003$). Les mêmes résultats étaient observés pour le strain circonférentiel global. Le strain circonférentiel global était de $-16.4 \pm 5.8\%$ chez les RAo et $-17.9 \pm 4.5\%$ dans les CMH ($P=0.36$). A l'effort, le strain circonférentiel global était de $-13.8 \pm 4.1\%$ dans les RAo et de $-18.6 \pm 5.3\%$ dans les CMH ($P=0.011$). La post-charge était plus élevée à l'effort chez les patients avec RAo que chez les CMH.

Conclusion : Malgré des caractéristiques au repos similaires, les déformations longitudinales et circonférentielles VG à l'effort sont plus basses chez les patients avec RAo modéré à sévère en comparaison avec des CMH. La plus grande post-charge observée chez les RAo conduit à une diminution de la réserve contractile.

Strain Analysis during Exercise in Patients with Left Ventricular Hypertrophy: Impact of Etiology

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Background: Hypertrophic cardiomyopathy (HCM) and aortic stenosis (AS) may influence left ventricular (LV) systolic function, despite preservation of LV ejection fraction. The aim of this study was to determine the relative importance of cardiac afterload and myocardial hypertrophy in the potential dysfunction of myocardial deformation, at rest and during standardized exercise.

Methods: Patients with moderate to severe ($\leq 1.5 \text{ cm}^2$) asymptomatic AS and patients with HCM in sinus rhythm were prospectively studied using resting and exercise echocardiography during submaximal exercise. Myocardial deformations were assessed using two-dimensional strain. Exclusion criteria were altered LV ejection fraction ($< 50\%$), coronary artery disease, intra-LV obstruction $> 30 \text{ mm Hg}$ at rest, diastolic LV thickness $\geq 30 \text{ mm}$, and New York Heart Association class $> \text{II}$. Thus, 50 patients (25 with AS, 25 with HCM) were selected and matched for age, sex, rest and exercise blood pressure, degree of LV hypertrophy (defined by maximal wall thickness), and LV ejection fraction.

Results: Mean resting global longitudinal strain (GLS) was $-14.9 \pm 4.7\%$ in patients with AS and $-16.1 \pm 3.9\%$ in those with HCM ($P = .30$). During exercise (mean heart rate, $110 \pm 10 \text{ beats/min}$), mean GLS was $-13.9 \pm 4.2\%$ in patients with AS and $-18.1 \pm 5.4\%$ in those with HCM ($P = .004$). GLS decreased in patients with AS but increased in those with HCM (ΔGLS , $0.9 \pm 3.1\%$ and $-1.9 \pm 3.2\%$, respectively, $P = .003$). The same results were observed for global circumferential strain. Mean resting global circumferential strain was $-16.4 \pm 5.8\%$ in patients with AS and $-17.9 \pm 4.5\%$ in those with HCM ($P = .36$). During exercise, mean global circumferential strain was $-13.8 \pm 4.1\%$ in patients with AS and $-18.6 \pm 5.3\%$ in those with HCM ($P = .011$). Afterload was higher, particularly during exercise, in patients with AS than in those with HCM.

Conclusions: Longitudinal and circumferential LV deformation during exercise was lower in patients with AS compared with those with HCM, despite similar resting characteristics. The greater afterload observed in patients with AS led to reduced contractile reserve. (*J Am Soc Echocardiogr* 2013;26:1163-9.)

Keywords: Left ventricular hypertrophy, Aortic stenosis, Hypertrophic cardiomyopathy, Strain, Longitudinal function, Exercise echocardiography

Two-dimensional (2D) strain has been validated as a new, easy, and fast method to analyze myocardial deformation. Abnormalities of 2D strain have been validated as a prognostic factor in a large number of cardiac diseases, including systolic heart failure,^{1,2} myocardial infarction,³ and aortic stenosis (AS).⁴⁻⁶ Two-dimensional strain has

also been proposed as an additional tool for differentiation between physiologic and pathologic left ventricular (LV) hypertrophy (LVH).^{7,8}

However, the determinants of LV longitudinal dysfunction remain controversial. In patients with AS, LV longitudinal function studied by echocardiography correlates with the degree of LVH.⁹ Fibrosis and myocardial fiber disarray have been reported to alter longitudinal function in patients with LVH.^{10,11} We previously reported that LV longitudinal function is blunted in patients with AS and that it is emphasized by an increase in afterload generated by standardized exercise.¹²

To describe the relative effects of afterload and of myocardial hypertrophy on the three components of the myocardial deformation (longitudinal, radial, and circumferential), we compared 2D strain parameters in patients with AS and those with hypertrophic cardiomyopathy (HCM) with the same echocardiographic degree of LVH. These parameters were recorded both at rest and during standardized submaximal exercise, performed to emphasize an increase in afterload. We expected that afterload would be more

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0894-7317/\$36.00

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<http://dx.doi.org/10.1016/j.echo.2013.06.002>

Abbreviations

AS = Aortic stenosis
GCS = Global circumferential strain
GLS = Global longitudinal strain
HCM = Hypertrophic cardiomyopathy
LV = Left ventricular
LVESMWS = Left ventricular end-systolic meridional wall stress
LVESV = Left ventricular end-systolic volume
LVH = Left ventricular hypertrophy
2D = Two-dimensional

elevated and would thus alter significantly the myocardial deformation in patients with AS compared with those with HCM.

METHODS**Study Population**

From February 2007 to January 2011, we prospectively and consecutively enrolled 150 patients with moderate to severe AS, along with 40 patients with HCM.

All patients were in New York Heart Association class I or II, were in sinus rhythm, and had normal LV ejection fractions ($\geq 50\%$) as calculated by 2D echocardiography. No patient had a history of coronary artery

disease. All presented with good echocardiographic windows and were able to perform exercise tests.

In the AS group, all patients demonstrated moderate to severe AS, defined by an aortic valve area $\leq 1.5 \text{ cm}^2$.¹³ In all cases, no more than mild associated other valve lesions were noted. In the HCM group, all patients had HCM, defined by recent guidelines.¹⁴ In this group, exclusion criteria were resting intra-LV pressure gradient $> 30 \text{ mm Hg}$ or diastolic LV thickness $\geq 30 \text{ mm}$.

All patients included underwent clinical examinations, 12-lead electrocardiography, resting echocardiography, and submaximal exercise echocardiography. From these two populations, 25 patients with AS and 25 with HCM were selected and matched according to age, gender, resting and exercise blood pressure, level of LV hypertrophy (defined by maximal wall thickness), and LV ejection fraction.

This study was approved by the hospital ethics committee and was conducted in accordance with the Declaration of Helsinki. All patients gave informed consent.

Study Protocol

All patients underwent clinical examinations, resting arterial blood pressure measurements (Dinamap Procare Auscultatory 100; GE Healthcare, Milwaukee, WI), resting 12-lead electrocardiography, and resting and exercise transthoracic echocardiography (Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway).

Patients underwent standard exercise echocardiography using an integrated electromagnetic cycle ergometer tilt table (Ergometrics, Lynnwood, WA). The initial workload was 30 W, with 20-W increments every 2 min until a stable heart rate of 100 to 120 beats/min was obtained. The pedaling rate was fixed at 60 rpm. As previously validated, echocardiographic exercise data were recorded at a submaximal stage with a stable heart rate of 100 to 120 beats/min.¹⁵ Exercise tests were interrupted in case of typical chest pain, severe limiting breathlessness, dizziness, muscular exhaustion, severe hypertension (systolic blood pressure $\geq 250 \text{ mm Hg}$), or significant ventricular arrhythmia. Exercise was followed by an active (2 min, 30 W, 60 rpm) and then a passive (4 min) recovery phase. An electrocardiogram was recorded continuously, and blood pressure was measured every 2 min during both exercise and recovery.

Echocardiography

Echocardiography was performed using standard acquisitions in the parasternal, apical, and subcostal views. Recordings were made both at rest and during the exercise test on a Vivid 7 machine.¹⁵ All resting and exercise data were stored on a workstation for offline analysis (EchoPAC; GE Vingmed Ultrasound AS). Analysis was performed offline on the EchoPAC workstation by two experienced echocardiographers (F.S., E.D.). For each patient, conventional analysis of the echocardiogram preceded the 2D strain analysis.

For each measurement, at least two cardiac cycles were averaged. LV diameters and wall thicknesses were assessed using M-mode imaging; concentric LV hypertrophy was defined as (interventricular septal thickness in diastole + posterior wall thickness in diastole)/LV end-diastolic diameter ratio > 0.42 .¹⁶ Aortic valve area was calculated using the continuity equation; mean and maximum transaortic gradients were obtained using continuous-wave Doppler. LV end-diastolic volume, LV end-systolic volume (LVESV), and LV ejection fraction were measured using the biplane method of disks. Peak E-wave and A-wave velocities of mitral inflow were measured using pulsed-wave Doppler. Doppler tissue imaging was recorded at the level of the septal and lateral mitral annulus. Peak velocities during systole and early (e') diastole were calculated first separately and then averaged. The E/e' ratio and Pr/Vol (IE/e' ratio/LV end-diastolic volume) were subsequently calculated.

LV end-systolic meridional wall stress (LVESMWS) was estimated as $0.334 \times \text{LV pressure} \times \text{LV diameter in systole/posterior wall thickness in systole} [1 + (\text{posterior wall thickness in systole/LV diameter in systole})]$, where LV pressure is estimated LV pressure (systolic blood pressure + mean aortic pressure gradient).¹⁷

Strain measurement was based on the speckle-tracking approach: to complete the analysis of LV systolic function, global longitudinal, circumferential, and radial myocardial deformation was evaluated from standard 2D images (frame rates $\geq 70 \text{ frames/sec}$) using 2D strain software (EchoPAC). In brief, by tracing the endocardial borders on an end-systolic frame, the software automatically tracked the contour on the subsequent frames. Adequate tracking was verified in real time and was manually corrected, if necessary.

Global longitudinal strain (GLS) was the average of the segment strains from the apical four-chamber view (Figures 1 and 2). Global radial strain and global circumferential strain (GCS) were the averages of the segment strains in the mid parasternal short-axis view. The image acquisition frame rate was 60 to 90 Hz (mean, 75 Hz).

The readers of the echocardiograms were, obviously, able to recognize patients with and without AS. But they were blinded to the results of the exercise stress tests. They did not have any clinical, electrocardiographic, or blood pressure data when reading the echocardiograms.

Strain values were indexed to LVESV to take into account LV geometric modifications induced by both pathologic conditions. Resting and exercise values and the Δ value between rest and exercise were calculated.

Statistical Analysis

Data are expressed as mean \pm SD or as percentages unless otherwise specified. Data were analyzed using parametric statistics after mathematical confirmation of normal distribution using Shapiro-Wilk tests. Group (AS vs HCM) comparisons for categorical variables were obtained using χ^2 tests and for continuous variables using one-way analysis of variance with Bonferroni's test when necessary. Correlations were determined between deformation and afterload

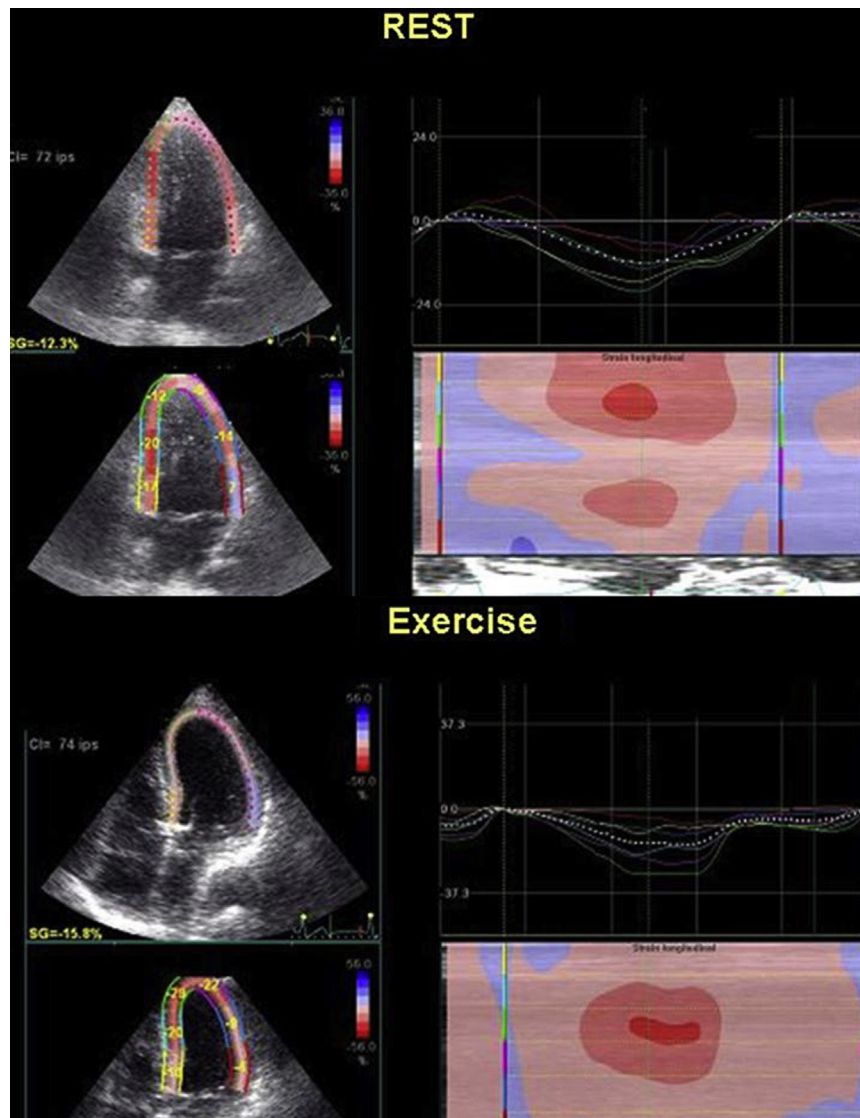


Figure 1 Example of resting and exercise longitudinal strain in a patient with AS. There was an increase in longitudinal strain during exercise.

parameters. Then, a multivariate linear regression was used to identify the independent predictors of alteration in exercise longitudinal and circumferential strain. We used a forward elimination procedure with the other variables. P values $< .05$ were considered statistically significant. Statistical analysis was performed using SPSS version 15 (SPSS, Inc., Chicago, IL).

RESULTS

Demographic and Hemodynamic Parameters

As expected, there was no significant difference in age, gender, resting and exercise systolic blood pressure, and exercise load between patients with AS and those with HCM.

HCM was revealed by an arrhythmic event (palpitation, documented atrial fibrillation, or ventricular tachycardia; 24%), dyspnea (32%), stroke (20%), or screening of an asymptomatic patient (competitive sport participation or family screening of relatives with HCM; 24%). Thirty-six percent patients had family histories of

HCM. At inclusion, 56% of patients with HCM and 92% of those with AS were in New York Heart Association class I ($P = .0037$; Table 1).

There was no difference in cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking). Treatments were not different between groups, except for a significantly more frequent use of β -blockers in the HCM group (Table 1). Therefore, resting heart rates were lower in patients with HCM, but there was no difference during submaximal exercise (Table 1). Although many patients were chronically treated for hypertension, all had normal rest blood pressures at the time of examination (Table 1).

By definition, aortic valve area in patients with AS was reduced ($1.01 \pm 0.2 \text{ cm}^2$), with the mean LV-aortic pressure gradient increased ($50.8 \pm 19.9 \text{ mm Hg}$).

No adverse events occurred during submaximal exercise testing. In only two patients with HCM was exercise LV obstruction observed (peak LV gradient $\geq 30 \text{ mm Hg}$). In patients with HCM, the maximal intraventricular pressure gradient was $6.1 \pm 3.9 \text{ mm Hg}$ at rest and increased to $14.1 \pm 10.9 \text{ mm Hg}$ at exercise. There was an abnormal

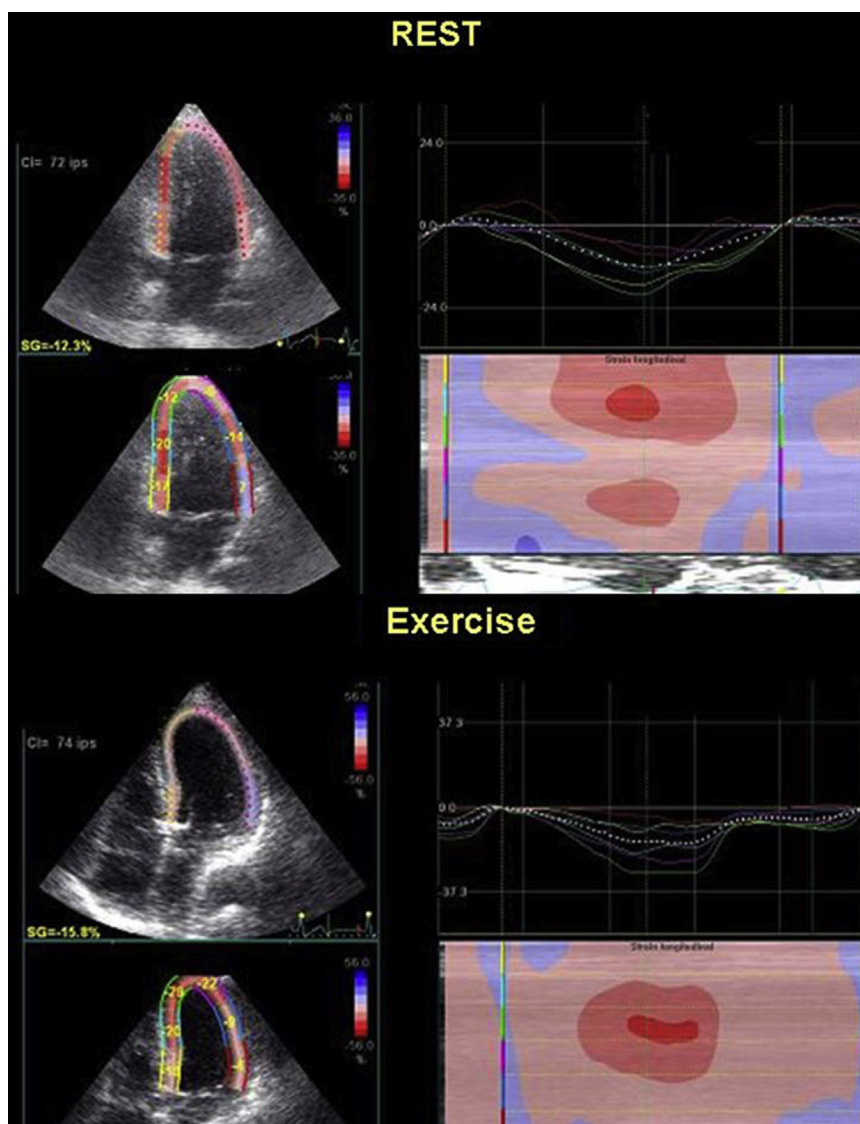


Figure 2 Example of resting and exercise longitudinal strain in a patient with HCM. There was no increase in longitudinal strain during exercise.

response in blood pressure (decrease or flat response with an increase of blood pressure < 20 mm Hg) in 28.5% of patients with HCM and in 21.7% of those with AS, with no significant difference between groups ($P = .73$).

Cardiac Hypertrophy Patterns

LV end-diastolic diameter and LV volumes were greater in patients with AS than those with HCM (Table 2). However, there was no significant difference in ventricular wall thicknesses between groups. Both groups demonstrated concentric LVH remodeling, but because of the larger LV end-diastolic diameter, the (interventricular septal thickness in diastole + posterior wall thickness in diastole)/LV end-diastolic diameter ratio was lower in the AS group ($P = .001$).

Diastolic Parameters

Resting diastolic parameters were similar in both groups (Table 3); however, with exercise, the E/e' and Pr/Vol ratios were significantly

higher in patients with HCM than in those with AS ($P = .04$ and $P = .0001$, respectively).

Systolic Parameters

Resting systolic parameters were similar between groups (Tables 4 and 5), with LV ejection fractions increasing similarly during exercise in both groups (Table 4). The global radial component of strain decreased in both groups during exercise, without a significant difference, for both absolute and Δ values (Table 4). Adaptations of the longitudinal and circumferential strain components were different between patients with AS and those with HCM. Indeed, the mean absolute value of GLS was lower in patients with AS than in those with HCM. Moreover, GLS decreased in patients with AS and increased in those with HCM (Δ GLS, $0.9 \pm 3.1\%$ vs $-1.9 \pm 3.2\%$, respectively, $P = .003$; Table 4). Last, absolute values of GCS decreased in patients with AS and increased in those with HCM, but no difference was observed for Δ values between the groups (Δ GCS, $2.2 \pm 8.3\%$ vs $-1.0 \pm 5.2\%$, respectively, $P = .11$; Table 4).

Table 1 Demographic, hemodynamic, and workload parameters

Parameter	AS (n = 25)	HCM (n = 25)	P
Age (y)	56 ± 12	50 ± 13	.09
Men	22	22	—
Hypertension	40%	52%	.39
Diabetes	12%	0%	.07
Dyslipidemia	28%	52%	.08
Smoking	32%	36%	.77
Medications			
β-blockers	4%	64%	<.0001
ACE inhibitors/ARBs	28%	44%	.23
Diuretics	16%	20%	.71
Statins	28%	52%	.08
ICD	0%	12%	.23
NYHA class			
I	92%	56%	.0037
II	8%	44%	
Systolic BP (mm Hg)			
Resting	139 ± 22	133 ± 15	.26
Exercise	171 ± 29	167 ± 31	.67
HR (beats/min)			
Resting	74 ± 12	60 ± 10	<.0001
Exercise	109 ± 7	108 ± 11	.66
Maximal workload (W)	110 ± 31	103 ± 48	.51

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; HR, heart rate; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association.

Data are expressed as mean ± SD, as numbers, or as percentages.

Table 2 Resting echocardiographic baseline parameters

Parameter	AS (n = 25)	HCM (n = 25)	P
IVSd (mm)	14.7 ± 1.9	15.8 ± 2.3	.07
PWd (mm)	13.9 ± 2.1	14.4 ± 1.8	.29
LVEDD (mm)	49.1 ± 6.7	41.8 ± 7.9	.0004
(IVSd + PWd)/LVDd	0.59 ± 0.09	0.76 ± 0.22	.001
LVEDV (mL)	129.8 ± 49	94.8 ± 28.3	.003
LVESV (mL)	51.7 ± 31.0	31.5 ± 12.5	.003

IVSd, Interventricular septal thickness in diastole; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; PWd, posterior wall thickness in diastole.

Data are expressed as mean ± SD.

Resting indexed strain component values for LVESV were not different between groups (Table 5). During exercise, both GLS/LVESV and GCS/LVESV were significantly lower in patients with AS than in those with HCM, but no difference was noted for global radial strain/LVESV.

Afterload Parameters

LVESMWS was significantly higher in patients with AS than in those with HCM both at rest (170.6 ± 34.0 vs 106.3 ± 25.2 mm Hg, $P < .0001$) and during exercise (195.7 ± 44.5 vs 125.0 ± 35.7 mm Hg, $P < .0001$). For the whole population, LVESMWS was positively

Table 3 Comparison of LV diastolic function parameters

Parameter	AS (n = 25)	HCM (n = 25)	P
Rest			
E/A ratio	1.05 ± 0.64	1.43 ± 0.87	.08
e' (cm/sec)	8.66 ± 1.99	8.76 ± 2.06	.86
E/e' ratio	9.63 ± 3.11	9.63 ± 4.28	.99
Pr/Vol (mL ⁻¹)	0.08 ± 0.03	0.12 ± 0.11	.07
Exercise			
E/A ratio	2.1 ± 1.57	1.44 ± 1.07	.15
e' (cm/sec)	14.32 ± 4.33	10.46 ± 2.70	<.001
E/e' ratio	9.71 ± 2.82	11.80 ± 2.93	.04
Pr/Vol (mL ⁻¹)	0.08 ± 0.04	0.15 ± 0.07	.0001

Data are expressed as mean ± SD.

Table 4 Parameters of LV systolic function

Parameter	AS (n = 25)	HCM (n = 25)	P
LVEF (%)			
Rest	64.1 ± 9.6	67.3 ± 8.2	.21
Exercise	68.0 ± 9.5	68.2 ± 8.6	.96
Δ	3.9 ± 9.4	0.9 ± 10.9	.30
GLS (%)			
Rest	-14.9 ± 4.7	-16.1 ± 3.9	.30
Exercise	-13.9 ± 4.2	-18.1 ± 5.4	.004
Δ	0.9 ± 3.1	-1.9 ± 3.2	.003
GRS (%)			
Rest	38.5 ± 18.3	39.2 ± 19.0	.91
Exercise	33.1 ± 12.8	34.8 ± 16.7	.77
Δ	1.0 ± 9.2	-5.2 ± 14.1	.20
GCS (%)			
Rest	-16.4 ± 5.8	-17.9 ± 4.5	.36
Exercise	-13.8 ± 4.1	-18.6 ± 5.3	.011
Δ	2.2 ± 8.3	-1.0 ± 5.2	.11

GRS, Global radial strain; LVEF, LV ejection fraction.

Data are expressed as mean ± SD.

Table 5 LV systolic function normalized to LVESV

Parameter	AS (n = 25)	HCM (n = 25)	P
GLS/LVESV (%)			
Rest	-0.43 ± 0.32	-0.61 ± 0.33	.057
Exercise	-0.43 ± 0.26	-0.79 ± 0.41	<.001
Δ	0.01 ± 0.19	-0.18 ± 0.29	.009
GCS/LVESV (%)			
Rest	-0.41 ± 0.32	-0.70 ± 0.43	.025
Exercise	-0.36 ± 0.26	-0.91 ± 0.74	.019
Δ	-0.01 ± 0.14	-0.22 ± 0.54	.21
GRS/LVESV (%)			
Rest	1.02 ± 0.88	1.50 ± 0.96	.11
Exercise	0.90 ± 0.72	1.50 ± 1.03	.089
Δ	0.13 ± 0.39	-0.04 ± 1.01	.61

GRS, Global radial strain; LVEF, LV ejection fraction.

Data are expressed as mean ± SD.

correlated with GLS/LVESV and GCS/LVESV at rest ($r = 0.40$, $P = .007$, and $r = 0.40$, $P = .02$) and during exercise ($r = 0.41$, $P = .01$, and $r = 0.54$, $P = .002$). LVESMWS was positively correlated with global radial strain/LVESV only during exercise ($r = -0.42$, $P = .02$).

At multivariate analysis (including age, etiology of LVH, exercise LVESMWS, exercise systolic blood pressure, exercise heart rate, and use of β -blockers), AS was the only predictor of decreased exercise GLS ($r = 0.33$, $P = .041$), and LVESMWS was the only predictor of decreased exercise GCS ($r = 0.56$, $P = .002$).

DISCUSSION

LV hypertrophy induced by cardiac diseases presents both structural and functional alterations.⁹ The present study demonstrates that despite close resting echocardiographic characteristics in LVH induced by AS and HCM, moderate dynamic exercise reveals specific functional adaptations depending on the mechanistic cause of LVH. Indeed, during submaximal exercise, longitudinal and circumferential LV deformations were dramatically decreased in patients with AS compared with those with HCM. Afterload was more elevated in patients with AS, in that LVESMWS was significantly higher in patients with AS than those with HCM, both at rest and during exercise. As a result, it appears that afterload has a major impact on exercise myocardial functional depression, especially circumferential deformation, even if other causal mechanisms associated with LVH, such as myocardial fibrosis and/or disarray, are also involved.⁹

Clinical Value of Myocardial Deformations

Two-dimensional echocardiographic speckle-tracking allows LV myocardial deformation components to be easily examined. Global strain is affected by many pathologic processes and is a relevant parameter for clinical practice. The quality of myocardial longitudinal strain has been validated as a prognostic parameter in patients with AS, those with systolic heart failure, and those who have had myocardial infarctions.¹⁻⁶ Weidemann *et al.*¹⁰ demonstrated that LV deformation was depressed in patients with AS and that longitudinal systolic function had an impact on clinical outcomes. The preoperative prognostic value of GLS in patients with AS was also confirmed by Kearney *et al.*¹⁸

Determinants of Myocardial Deformation Alteration

Strain is not a direct measurement of regional and/or global myocardial contractility. Yet strain measurements are influenced by load, as well as by the geometric and histologic characteristics of the heart.^{9,19-21}

The present investigation emphasizes this load dependence, with an observed correlation between markers of afterload (LVESMWS) and GLS or GCS. GCS seems more affected than GLS by loading conditions, as demonstrated by the results of multivariate analysis. Data from our laboratory have previously demonstrated that alterations in circumferential strain are associated with low-flow AS and increased afterload.²² Corroboration of these data was also observed in an acute animal experiment.²³

In the present study, radial deformation was less influenced by afterload; this was not observed by Delgado *et al.*,⁵ demonstrating the normalization of this parameter after aortic valve replacement.

However, afterload is not the only determinant of myocardial deformation alteration. Indeed, Delgado *et al.*⁵ demonstrated that surgery improves GLS after aortic valve replacement, but still longitudinal strain was inferior to that in controls. GLS improved because of the diminution of afterload linked to the AS correction but was not normalized, because of myocardial fibrosis, which cannot be corrected operatively. In the same way, Weidemann *et al.*¹⁰ also demonstrated that longitudinal systolic function in patients with AS was sensitive to the severity of myocardial fibrosis. Our study emphasizes these findings: on multivariate analysis, afterload was the major predictor of a decrease in GCS, whereas GLS was more influenced by the etiology of LVH.

Impact of Exercise on Myocardial Deformation

The value of 2D strain analysis during exercise echocardiography has been previously validated in patients with heart failure with preserved ejection fractions.¹⁵ The clinical value of this evaluation has been recently underlined.¹⁹ We have previously demonstrated the value of submaximal dynamic exercise testing to reveal adaptive abnormalities of myocardial contractility in patients with AS in comparison with healthy subjects, despite a lack of abnormality at rest.¹² The present study demonstrates that moderate exercise echocardiography reveals myocardial contractility abnormalities, not observed at rest, between patients with similar patterns of LVH that are specific to the pathologic mechanism causing such LVH (in this case, AS and HCM). Indeed, strain decreased slightly in patients with AS and increased in those with HCM; constraints, particularly afterload associated with exercise, may help explain this observation.

With the present study, we confirm the correlation between exercise longitudinal and circumferential strain and afterload. These differences seem independent of geometry, as indexed values for LVESV show.

In the present study, we compared two etiologies of LVH that were very easy to distinguish. We could try to use exercise echocardiography in other etiologies of LVH to differentiate posthypertensive LVH from HCM, which is sometimes a difficult issue in clinical practice.

Limitations

The first limitation is linked to the difference in medications in both groups; indeed, there was significantly more frequent use of β -blockers in patients with HCM (64% vs 4%, $P < .0001$).

Palmieri *et al.*²⁴ showed that β -blockers (specifically bisoprolol) reduce longitudinal systolic function in patients with hypertension. Thus, in our study, we can suppose that β -blockers may also have decreased longitudinal strain values, which would not change our results; patients with HCM have contractile reserve even if they are treated with β -blockers.

The chronotropic negative effect of β -blockers exists at rest (resting heart rate, 74 ± 12 beats/min in patients with AS vs 60 ± 10 beats/min in those within HCM, $P < .0001$), but given our submaximal exercise protocol, there was no difference in exercise heart rate (109 ± 7 beats/min in patients with AS vs 108 ± 11 beats/min in those with HCM, $P = .66$).

We chose to perform longitudinal strain analysis only in the apical four-chamber view. Considering the difficulty of performing speckle-tracking during exercise, we chose to use only this view because of better image quality than in the three-chamber or two-chamber view.

Both global and regional longitudinal strain can be studied.⁴ The heterogeneity in peak regional strain might provide additive

information to global deformation. This was not the goal of the present study.

CONCLUSIONS

In two populations of patients with LVH (AS and HCM), sub-maximal exercise showed dramatic depressions of longitudinal and circumferential LV deformation in those with AS. These differences were not observed at rest. These observations, especially depression in circumferential strain, may be due mainly to the higher afterload in AS that was emphasized by exercise.

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3.2. Intérêt de l'échocardiographie d'effort

3.2.2 Comme outil de pronostique

Nous avons montré dans les études précédentes que l'échocardiographie d'effort permettait de mieux caractériser les CMH. Les recommandations actuelles sur la stratification des CMH ne prennent pas en compte les données de l'échocardiographie d'effort ⁹. Nous avons donc voulu évaluer l'intérêt pronostique des données obtenues par cette nouvelle modalité d'imagerie.

Compte tenu de la difficulté d'obtenir des données pronostiques sur une faible population, nous avons dans ce travail inclus l'ensemble de nos sujets avec CMH, sans tenir compte de l'effet potentiel de l'activité physique.

Apport du candidat dans ce travail

Les données issues de ce travail ont été obtenues grâce à la base prospective des CMH réalisée dans le cadre de ce travail de thèse. Relecture et correction du manuscrit.

RESUME

Objectifs : L'échocardiographie de repos a un rôle majeur dans le diagnostic et la stratification du risque des cardiomyopathies hypertrophiques (CMH). En effet, une dilatation de l'oreillette gauche, une hypertrophie ventriculaire gauche (VG) sévère et un gradient intra VG ≥ 50 mm Hg sont décrits dans les récentes recommandations comme étant des facteurs de risque de mort subite. Par contre, les données de l'échocardiographie d'effort ne jouent qu'un rôle limité dans l'évaluation du pronostic compte tenu de données encore insuffisantes dans la littérature. En pratique clinique, la présence d'un gradient intra VG, d'une insuffisance mitrale ou la pression pulmonaire à l'effort sont des paramètres dont l'évaluation à l'effort pourrait être pertinente. Ainsi, l'objectif de ce travail était de déterminer si l'étude des modifications des fonctions myocardiques et valvulaires induites par l'effort pouvait améliorer la stratification du risque dans les CMH.

Méthodes et résultats : Des patients avec CMH et fraction d'éjection préservée ont bénéficiés d'une échocardiographie d'effort (incluant l'évaluation de la fonction myocardique, de l'obstruction intra VG et des régurgitations valvulaires) à l'inclusion, puis ont été suivis sur le plan clinique sur une durée médiane de 29.3 mois. Le critère de jugement primaire était un critère combiné incluant décès toute cause, arrêt cardio-respiratoire et hospitalisation pour événement cardiologique. 126 patients ont été inclus de manière consécutive, 18 patients ont atteint le critère de jugement primaire. Une régression de Cox univariée a montré qu'un gradient intra VG ≥ 50 mmHg (HR=3.31, P=0.01) et une fuite mitrale significative à l'effort ($\geq 2/4$) (HR=3.64, P<0.01) étaient associés avec le critère de jugement primaire. Les patients avec une fuite mitrale significative avaient un gradient intra VG de repos et d'effort plus important (P=0.001 and P=0.001) et des oreillettes gauches plus larges (P<0.001).

Conclusion: Une fuite mitrale significative à l'effort semble être un élément prédictif majeur dans la CMH et est associée avec des gradients intra VG de repos et d'effort plus élevés.



Impact of exercise-induced mitral regurgitation on hypertrophic cardiomyopathy outcomes

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Received 10 May 2015; accepted after revision 6 September 2015

Aims

Rest echocardiography plays a role in hypertrophic cardiomyopathy (HCM) diagnosis and risk stratification because left atrial enlargement, severe left ventricle (LV) hypertrophy, and rest LV outflow tract (LVOT) gradients ≥ 50 mmHg are sudden cardiac death risk factors that have been highlighted in recent guidelines. Conversely, the lack of evidence makes that exercise-echocardiography findings play a limited role. In clinical practice, LVOT gradient, but also mitral regurgitation (MR) or pulmonary pressure, seems relevant parameters to look for, during the exercise. Therefore, we sought to determine whether exercise-induced changes in myocardial and valvular functions could improve HCM risk stratification.

Methods and results

Consecutive primitive HCM patients with a preserved LV ejection fraction underwent standardized exercise echocardiography (including the assessment of myocardial function, dynamic left intraventricular gradient, and valvular regurgitations) at baseline and were clinically followed for a median of 29.3 months. The primary endpoint was a composite criterion that included death from any cause, cardiorespiratory arrest, and hospitalization for a cardiovascular event. A total of 126 patients were included. Eighteen patients reached the primary endpoint. According to univariate Cox regression analysis, exercise LVOT gradient ≥ 50 mmHg [hazard ratio (HR) = 3.31, $P = 0.01$] and significant ($\geq 2/4$) exercise MR (HR = 3.64, $P < 0.01$) were associated with the primary endpoint. Patients with significant MR had significantly higher rest and exercise LVOT gradients ($P = 0.001$ and $P = 0.001$) and larger left atria volumes ($P < 0.001$).

Conclusion

Significant exercise-induced MR appears to significantly impact the prognoses of HCM patients, and it is also associated with higher LVOT rest and exercise gradients.

Keywords

hypertrophic cardiomyopathy • prognosis • exercise echocardiography • exercise-induced mitral regurgitation

Introduction

Hypertrophic cardiomyopathy (HCM) is regarded as the most common genetic cardiovascular disorder¹; it exhibits an autosomal dominant Mendelian pattern and age-related (and incomplete) penetrance. The pathophysiology of HCM is complex and continues to be a source of controversy in the literature.² Echocardiography plays a major diagnostic role in this disease management.³

HCM is frequently compatible with a normal life expectancy.^{4,5} But, subgroups at risk for complications exist.¹ Sudden cardiac death

(SCD), which is the most worrisome and visible complication of HCM, but is not easily predictable. The following major features have been proposed for their value in distinguishing patients with an increased risk of SCD in adults: (i) age, (ii) non-sustained ventricular tachycardia (≥ 3 consecutive ventricular beats at ≥ 120 bpm lasting < 30 s), (iii) maximum left ventricle (LV) wall thickness ≥ 30 mm, (iv) family history of SCD at a young age, (v) unexplained syncope, (vi) left atrium diameter (LAD), and (vii) left ventricle outflow tract obstruction (LVOTO) at rest.⁶ According to latest guidelines, calculation of the SCD risk score using these seven features is recommended.⁷

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Exercise-echocardiography findings play only a limited role in recommendations certainly because of the lack of evidence.⁸ Interestingly, in the current European Society of Cardiology (ESC) guidelines,⁶ an LVOTO gradient is ≤ 50 mmHg at rest justify an exercise echocardiography, only in symptomatic patients to evaluate LVOTO during exercise. The exam should thus focus on LVOTO but the interaction between the myocardium, the valves and the blood flows looks too complex for just looking for LVOTO. In clinical practice, LVOT gradient, but also mitral regurgitation (MR) or pulmonary pressures, seems relevant parameters to look for, during the exercise. Therefore, we sought to determine whether exercise-induced changes not only in myocardial but also in mitral valvular regurgitations could improve HCM risk stratification.

Patients and methods

Patients

We prospectively included HCM patients who were admitted to our regional HCM Competence Center, from October 2009 to May 2013. Patients were prospectively evaluated at baseline using clinical parameters, as well as echocardiography at rest and during a standardized exercise. The following inclusion criteria were applied: patients suffering from HCM with LV hypertrophy, as defined by the current American College of Cardiology Foundation/American Heart Association,⁹ in the absence of another cardiac or systemic disease capable of producing the magnitude of LV hypertrophy observed. Patients with (i) permanent atrial fibrillation (AF), (ii) a history of coronary artery disease, (iii) a history of cardiac surgery (myomectomy or alcohol septal ablation), or (iv) inadequate acoustic windows ($n = 4$) were excluded from the analysis.

All patients provided informed consent to participate in this study, which was performed in accordance with the principles outlined in the Declaration of Helsinki on research in human subjects (CNIL declaration n°909378).

Exercise echocardiography

Medications were not withdrawn before the exams. Exercise echocardiography was conducted in accordance with EACVI recommendations.⁴ Following the clinical examination, arterial blood pressure measurements, and 12-lead electrocardiogram (ECG), the patients underwent exercise echocardiography in a standard semi-supine position with a slight left lateral tilt (bicycle tilted to $\sim 50^\circ$), on a tilting bicycle ergometer (Ergoline GmbH, General Electric, Bitz, Germany). Using a Vivid 9 ultrasound system with an M4S transducer (GE Healthcare, Horten, Norway), an experienced (level 3) operator¹⁰ performed the exercise examination. Testing started with an initial workload of 30 W, and the workload increased in 30 W increments every 2 min. The pedalling rate was 60 rotations per minute. ECG results were recorded continuously, and blood pressure was measured every 2 min. Exercise was interrupted in case of significant arrhythmia, severe hypertension (systolic BP > 240 mmHg or diastolic BP > 110 mmHg), hypotensive response (decrease > 20 mmHg from baseline), or limiting symptoms. Two-dimensional echocardiography was performed in standard parasternal and apical views at baseline and at peak exercise.

We calculated the number of metabolic equivalents (METs) for each patient (in terms of the METs achieved during exercise and the expected results based on age and sex). To predict METs, we used the Veterans Affairs cohort formula for men and the St James Take Heart Project

formula for women. These formulas reportedly perform best in their ability to predict outcomes.¹¹ We then calculated the achieved/predicted METs ratio as described by Desai et al.¹²

We also calculated the 5-year probability of SCD in our population as described in the latest ESC guidelines.⁶

Echocardiographic measurements

Two-dimensional echocardiographic analyses were performed offline at baseline and during exercise by two experienced physicians who were unaware of each patient's clinical status. All measurements were performed according to recommendations of chambers quantification¹³ and diastolic function assessment.¹⁴ MR, if present, was graded (0–4) using the proximal isovelocity surface area (PISA) method as described in the European Association of Cardiovascular Imaging recommendations.¹⁵ During exercise and at rest, outflow velocities were measured using continuous-wave Doppler. Outflow gradients were automatically calculated from the flow velocity using the modified Bernoulli equation.¹⁶ Care was taken not to confuse LV outflow and MR flow. Systolic anterior motion (SAM) of the mitral valve was defined as a paradoxical motion of the anterior mitral valve leaflet towards the LVOT during systole.⁴

Deformation imaging indices

Three consecutive cardiac cycles were recorded and averaged, and the frame rate was set to 60–80 frames/s. The analysis was performed offline using customized software (EchoPAC PC BT12; GE Healthcare). Global longitudinal strain (GLS) of the LV has been measured according to the previous report.¹⁷ The LA endocardial border was also manually traced on the apical four-chamber view. After manual adjustment of a region of interest covering the full thickness of the myocardium, the software divided the LA into six segments and automatically scored the segmental tracking quality. The software rejected segments with inadequate image quality and excluded them from the analysis. Longitudinal strain curves were generated for each of the six LA segments in the four chambers. Global peak LA longitudinal strain during ventricular systole (ϵ_s) was then measured by averaging the values obtained from the six LA segments. The same tracing method was used to calculate the strain rate and to analyse the LA systolic peak of strain rate. A cardiologist with a level 3 in echocardiography, who was unaware of the patients' information, analysed all of the echocardiographic values (Figure 1).

Follow-up

After the initial evaluation, follow-up data were obtained in summer 2014. Data were collected from our hospital computer database; in case of missing data, the patient's cardiologist or general practitioner was contacted by phone or, if necessary, the patients themselves were contacted. The mean duration follow-up was determined using the most recent evaluation or the patient's date of death.

Endpoints

The primary clinical endpoint was a composite criterion including death from any cause, cardiorespiratory arrest, and hospitalization related to a cardiac event.

The secondary endpoint was a cardiorespiratory arrest (resuscitated or not) event [or judge as equivalent: justified shock from an implantable cardioverter-defibrillator (ICD)].

Statistical analysis

Continuous variables are presented as the mean \pm standard deviation or as the median [interquartile range] in case of skewness. Categorical

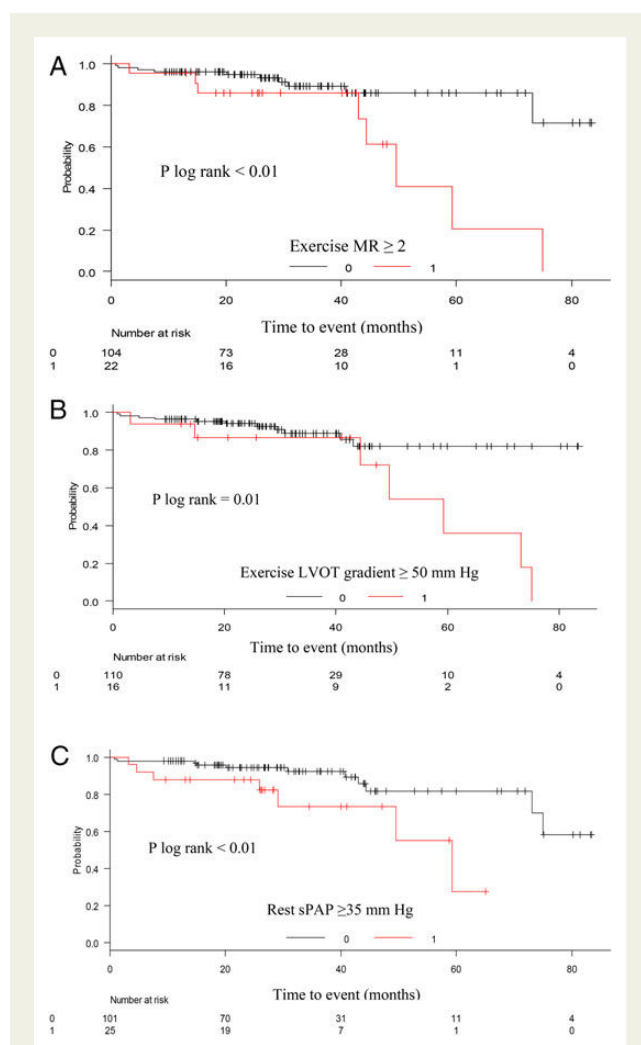


Figure 1 Kaplan–Meier primary event survival curves (log-rank test) in patients with exercise MR ≥ 2 vs. < 2 (A), exercise LVOT gradient ≥ 50 mmHg vs. < 50 mmHg (B), and rest sPAP ≥ 35 mmHg vs. < 35 mmHg (C). The small vertical lines in the survival curves indicate time points at which patients were censored.

data are summarized as frequency and percentages. We compared patients who reached endpoints and the others. The differences in baseline characteristics between the two groups were analysed with the Student's *t*-test, Mann–Whitney test, χ^2 or Fisher's exact test, as appropriate. Survival analyses were performed with two different tests; a univariate Cox proportional hazard regression analysis was performed to assess relationship between the different variables and the endpoints. We did a multivariate Cox regression for primary endpoint with stepwise selection based on the Akaike Information Criteria. Exercise MR and rest echocardiographic parameters selected with $P < 0.1$. That multivariable analysis was only 'informative' but, was of limited value because of the low number of events. Ten events are usually required for each variable included in a multivariable analysis. The other survival analysis was the building of survival curves according to the Kaplan–Meier method.

A *P*-value < 0.05 was considered statistically significant. All statistics were done with R (R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>).

Results

Patient population

A total of 126 patients were included in our study. The median follow-up time was 29.3 months, with an interquartile range of 24.3 months. The majority of patients was male (78%), with a mean age of 47 years. Eighteen patients reached the primary endpoint (14.2%). Seven patients presented with cardiorespiratory arrest: three died, two of an unknown cause, and one following a heart surgery for left-ventricular assistance device implantation. Three patients were successfully resuscitated following ventricular arrhythmia. One patient had an appropriate internal shock delivered by his ICD for ventricular fibrillation.

Eleven patients were hospitalized for cardiac-related events. Four patients were hospitalized for pulmonary oedema, two for a sinus node dysfunction requiring a pace maker, two for symptomatic AF, and one patient for chest pain. One patient presented a syncope and one patient suffered from a pulmonary embolism.

Echocardiography and primary endpoint

Significant exercise-induced MR (MR $\geq 2/4$) was present in 22 patients (20.9%). Exercise-induced MR but not rest MR was associated with primary endpoint, $P < 0.01$ and $P = 0.09$, respectively. Rest SAM, rest, and exercise LVOT gradient ≥ 50 mmHg were determinant of primary endpoint ($P = 0.02$, $P = 0.05$ and $P < 0.01$, respectively). Exercise-induced tricuspid regurgitation (TR) was not linked to the primary endpoint ($P = 0.41$), whereas TR-based estimation of the systolic pulmonary artery pressure (sPAP) at rest was a determinant of primary endpoint when a cut-off of 35 mmHg was used ($P = 0.04$). Achieved/predicted METs ratio was not associated with the primary endpoint ($P = 0.23$).

Secondary endpoint: cardiorespiratory arrest

The variables linked with the hard point (i.e. cardiorespiratory arrest) were the probability of SCD at 5 years, which was calculated according to the formula in the ESC guidelines ($P < 0.01$), significant exercise-induced MR ($P = 0.02$), exercise left atrial volume indexed (LAVi) ($P = 0.04$), and an exercise LVOT gradient ≥ 50 mmHg ($P = 0.04$) (Table 1).

Univariable Cox regression analysis

The study results are shown in Table 1. Exercise-induced MR ≥ 2 , rest sPAP ≥ 35 mmHg, and exercise LVOT gradient ≥ 50 mmHg were associated with the primary endpoint. Regarding cardiorespiratory arrest, exercise-induced MR was the only determining echocardiographic variable [hazard ratio (HR) = 4.7, $P = 0.04$]. Kaplan–Meier survival curves associated with primary endpoint and cardiorespiratory arrest are shown in Figures 1 and 2, respectively.

Exercise-induced MR and others echocardiographic parameters

Regarding the results of the prognosis importance of exercise-induced MR in our population, we studied the link between MR and others echocardiographic parameters. The results are shown in Table 2. There is a strong relationship between exercise-induced MR

Table 1 Univariable Cox regression

	Primary endpoint		Cardiorespiratory arrest	
	HR	P	HR	P
Clinical data				
Age	1.00 (0.97–1.04)	0.88	0.95 (0.90–1.01)	0.08
Men	1.5 (0.43–5.2)	0.52	0.60 (0.11–3.3)	0.56
Weight	1.03 (0.99–1.06)	0.09	1.01 (0.95–1.07)	0.76
Body surface area (m ²)	14.1 (1.13–176.5)	0.04	1.44 (0.02–80.4)	0.86
Follow-up duration (months)	1.00 (0.99–1)	0.06	0.99 (0.98–1.00)	0.03
Family history of HCM	0.31 (0.09–1.08)	0.07	0.3 (0.03–2.6)	0.27
Implanted defibrillator	0.77 (0.17–3.48)	0.73	3.2 (0.51–20.1)	0.21
Caucasian	0.40 (0.05–3)	0.37	1.4 (0.16–11.9)	0.77
History of hypertension	1.2 (0.43–3.2)	0.75	0.48 (0.05–4.26)	0.51
Angina	0.97 (0.27–3.51)	0.96	0.76 (0.08–7.12)	0.81
NYHA class	0.99 (0.44–2.3)	0.99	0.93 (0.22–3.9)	0.92
Medications				
VKA	2.96 (1.09–8.05)	0.03	2.13 (0.39–11.8)	0.38
Beta-blockers	4.14 (0.55–31.3)	0.17	∞ (0–∞)	0.99
Calcium channel blockers	2.26 (0.79–6.44)	0.13	0.89 (0.10–7.7)	0.91
ACE inhibitors/ARBs	3.13 (1.12–8.72)	0.03	4.4 (0.70–27.5)	0.11
Major risks factors for SCD				
Lipothymia/syncope	1.93 (0.63–5.93)	0.25	1.05 (0.12–9.07)	0.97
Familial SCD	0.40 (0.09–1.77)	0.23	0.64 (0.07–5.50)	0.68
LV hypertrophy (≥30 mm)	0 (0–∞)	0.99	0 (0–∞)	0.99
Non-sustained ventricular tachycardia	1.14 (0.37–3.55)	0.82	3.6 (0.73–18.3)	0.12
Left atrial diameter (mm)	1.08 (1.01–1.15)	0.02	1.05 (0.96–1.15)	0.32
Exercise parameters				
Achieved/predicted METs	0.99 (0.96–1.02)	0.66	0.98 (0.93–1.025)	0.37
LV function parameters				
Rest LVEF	1.01 (0.95–1.07)	0.74	1.05 (0.95–1.17)	0.34
Exercise LVEF	1.03 (0.98–1.08)	0.31	0.99 (0.92–1.07)	0.92
Rest SGL	0.95 (0.83–1.08)	0.48	0.93 (0.75–1.15)	0.50
Exercise SGL	0.94 (0.86–1.03)	0.20	0.98 (0.85–1.12)	0.72
LVOT parameters				
Rest LVOT gradient ≥50 mmHg	2.2 (0.72–6.8)	0.16	3.5 (0.67–18.03)	0.14
Exercise LVOT gradient ≥50 mmHg	3.31 (1.26–8.6)	0.01	3 (0.62–14.4)	0.17
Diastolic function				
LAVi rest	1.02 (0.99–1.05)	0.29	1.04 (0.99–1.09)	0.1
LAVi exercise	1.02 (0.99–1.5)	0.13	1.04 (0.99–1.08)	0.1
Mitral regurgitation				
Rest MR ≥2/4	1.96 (0.64–6)	0.23	1.05 (0.12–8.8)	0.97
Exercise MR ≥2/4	3.64 (1.4–9.3)	<0.01	4.72 (1.04–21.63)	0.04
RV parameters				
Rest sPAP ≥35 mmHg	3.60 (1.34–9.68)	0.01	1.8 (0.35–9.37)	0.48
SCD ESC risk score				
SCD at 5 years ≥5%	NA	NA	1.9 (1.36–2.7)	<0.01

HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; SCD, sudden cardiac death; VKA, vitamin K antagonist; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; LV, left ventricle; METs, metabolic equivalents; LVEF, left ventricle ejection fraction; GLS, global longitudinal strain; LVOT, left ventricle outflow tract; SAM, systolic anterior motion; LAVi, left atrial volume indexed; MR, mitral regurgitation; RV, right ventricle; sPAP, systolic pulmonary artery pressure.

and LVOT obstruction during exercise and at rest ($P = 0.001$). Half of patients with exercise-induced MR ($n = 12$) had a LOVT gradient ≥ 50 mmHg, whereas 6.2% of patients ($n = 7$) without

an exercise-induced MR had an LVOT gradient ≥ 50 mmHg ($P < 0.001$). Patients with exercise-induced MR had a larger LA (at rest and at exercise) and a reduced LA 2D strain ($P = 0.02$).

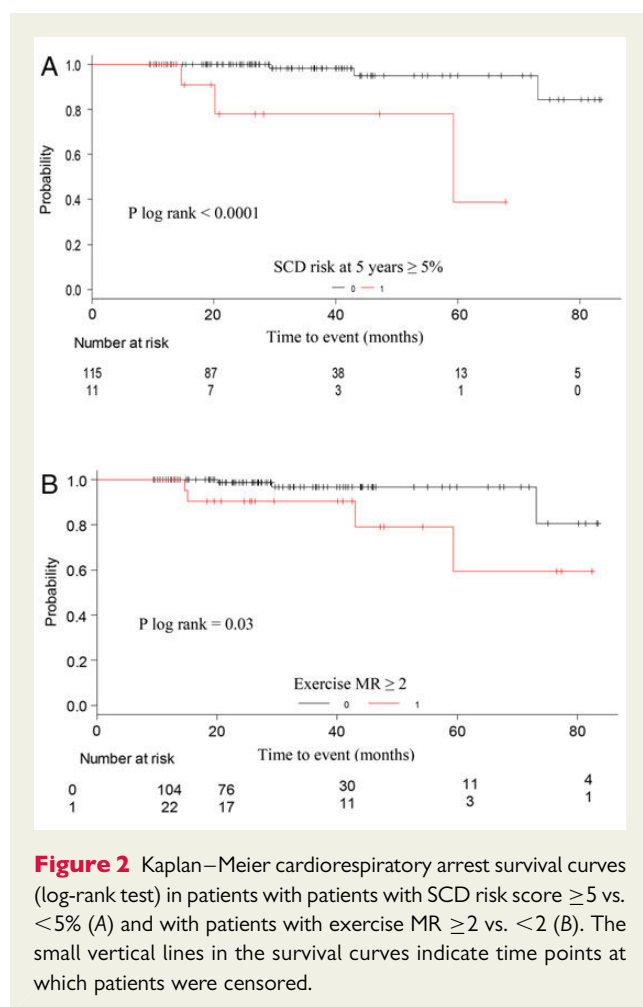


Figure 2 Kaplan–Meier cardiorespiratory arrest survival curves (log-rank test) in patients with patients with SCD risk score ≥ 5 vs. $< 5\%$ (A) and with patients with exercise MR ≥ 2 vs. < 2 (B). The small vertical lines in the survival curves indicate time points at which patients were censored.

Multivariable analysis

Table 3 is providing the result of a multivariable analysis supporting the prognostic value of the exercise-induced MR even if the number of event is low.

Discussion

Main results

Exercise echocardiography, actually used for a better assessment of the functional status of our patients, appeared to provide valuable prognostic information in HCM patients.

Exercise-induced LVOT gradient ≥ 50 mmHg and significant exercise-induced MR are strong predictors of cardiovascular events. Furthermore, exercise-induced MR was the only echocardiographic parameter associated with hard events such as cardiorespiratory arrests (or equivalent). The other predictor of this hard event in our population was the probability of SCD at 5 years calculated according to the latest ESC guidelines.⁶

Prognosis value of exercise echocardiography in the literature

In 2006, Maron *et al.*¹⁸ were the first to demonstrate the value of exercise echocardiography in studying LVOTO during exercise. Since, few studies have been published.

In a group of 426 HCM patients, using a composite endpoint of death, appropriate defibrillator discharge and hospitalization for heart failure, Desai *et al.*,¹² showed that the per cent of age–sex–predicted METs (the ratio achieved/predicted) and AF was predictive of outcome. But the authors did not find that any exercise echocardiographic variable was linked to patient outcomes. Following 239 HCM patients for 4 years, Peteiro *et al.*¹⁹ found that in baseline echocardiography, LAD predicted hard events. This relationship between LAD and prognosis has been found in numerous studies before,^{7,20–22} thus LAD is now included in the recent ESC SCD risk calculation guidelines.⁶ Our study confirms the predictive value of the LAD. Regarding exercise echocardiography, they found that moderate or greater exercise-induced MR was present in 28% of patients during exercise and was linked to exercise LVOTO. Patients reaching primary endpoints had more significant exercise-induced MR (47 vs. 26%) but this result was not significant ($P = 0.05$). Wall motion abnormalities (WMAs) were significantly more frequent in patients with hard events (31 vs. 5%, $P < 0.01$). Myocardial ischaemia could be the explanation of WMAs, as suggested in some studies.^{23,24} This has been confirmed by this latest study published in 2015 with a similar protocol.²⁵ Following 148 patients for a mean of 7.1 years, Peteiro *et al.* found that 23% of patients with events had WMA at exercise vs. 6% ($P = 0.005$) for patients without events. Perfusion defect area and late gadolinium enhancement in CMR were also associated with events. Exercise MR was not linked to events but again, exercise echocardiography was in fact post-exercise as images were acquired immediately after the exercise.

We performed images acquisition during exercise in a semi-supine bicycle and not in the post-exercise of a treadmill test. Indeed, workload tended to be higher with treadmill exercise in comparison with supine bicycle,²⁶ but sensitivity to the detection of ischaemia appeared to be better with peak exercise imaging than with post-exercise imaging.²⁷ Furthermore, when additional Doppler information is desired, supine bicycle exercise offers the advantage that information can be evaluated during exercise. Modesto *et al.*²⁸ demonstrated that compared with post-exercise image analysis, peak exercise images acquisition was superior in recognizing patients with exercise-induced pulmonary hypertension and MR. In fact, as soon as the exercise is stopped, while inotropism continued for a while, afterload decreases immediately, inducing rapid changes in left and right side heart pressure. These differences between the two exercise-echocardiography protocols can explain the different results. When looking for the highest METs achieved, standard treadmill testing with post-exercise image acquisition should be preferred, but when studying pressure, gradients, and regurgitation, peak imaging should probably be favoured. In the latest ESC HCM guidelines, exercise echocardiography *during exercise* is recommended.⁶

In our work, we did not found significant WMAs during exercise and, using recent 2D strain speckle tracking techniques,²⁹ we did not observe that patients with events demonstrated decreased LV systolic function at rest or during exercise. Recently, Reant *et al.*,³⁰ in 119 HCM patients followed for 19 months, showed that peak exercise LVOT gradient and rest GLS $< 15\%$ predicted outcomes (mainly dyspnoea or increase in NYHA class). Here, we did not found the independent prognostic value of GLS probably because of the difference in censored events during follow-up. GLS is probably more predictive of heart failure than of rhythmic events.

Table 2 Characteristics according to the presence of an MR or not

	All patients (n = 126)	Exercise MR <2 (n = 105)	Exercise MR ≥2 (n = 21)	P
Clinical data				
Age	47.41 ± 15.48	47.04 ± 15.65	49.29 ± 14.83	0.55
Men (%)	99 (78.1%)	85 (81%)	14 (66.7%)	0.15
Weight (kg)	75.6 ± 13.9	75.0 ± 12.9	78.8 ± 18.1	0.26
Body surface area (m ²)	1.86 ± 0.19	1.86 ± 0.19	1.89 ± 0.23	0.45
Follow-up duration (months)	29.3 [24.3]	28.6 [73.9]	39.9 [69.2]	0.08
Family history of HCM	42 (34.1%)	37 (36.3%)	5 (23.8%)	0.32
Implanted defibrillator	16 (12.7%)	11 (10.5%)	5 (23.8%)	0.14
Caucasian	109 (86.5%)	89 (84.8%)	20 (95.2)	0.30
History of hypertension	39 (31.0%)	37 (35.2%)	2 (9.5%)	0.02*
Angina	14 (10.4%)	12 (11.4%)	2 (9.5%)	1
NYHA class				0.02*
I	66 (52.4%)	60 (57.1%)	6 (28.6%)	
II	55 (43.7%)	42 (40%)	13 (61.9%)	
III	5 (4.0%)	3 (2.9%)	2 (9.5%)	
Medications				
VKA	17 (13.5%)	10 (9.5%)	7 (33.3%)	0.01*
Beta-blockers	95 (75.4%)	74 (70.5%)	21 (100%)	0.002*
Calcium channel blockers	17 (13.5%)	13 (12.4%)	4 (19%)	0.48
ACE inhibitors/ARBs	34 (27.0%)	27 (25.7%)	7 (33.3%)	0.59
Major risks factors for SCD				
Lipothymia/syncope	16 (51.9%)	13 (12.4%)	2 (9.5%)	1
Familial SCD	28 (20.7%)	25 (23.8%)	3 (14.3%)	0.40
LV hypertrophy (≥ 30 mm)	7 (5.2%)	5 (4.8%)	2 (9.5%)	0.33
Non-sustained ventricular tachycardia	18 (10.8%)	13 (12.4%)	5 (23.8%)	0.18
Left atrial diameter (mm)	52 ± 8	52 ± 7	57 ± 8	0.002*
Exercise parameters				
Achieved/predicted METs (%)	67 ± 21	69 ± 22	59 ± 16	0.05*
LV parameters				
Rest LVEF (%)	66 ± 8	66 ± 9	64 ± 14	0.23
Exercise LVEF (%)	72 ± 15	72 ± 17	66 ± 13	0.08
Rest GLS (%)	−15.2 ± 3.9	−15.70 ± 5.80	−14.70 ± 3.2	0.35
Exercise GLS (%)	−18.1 ± 5.3	−18.55 ± 7.58	−15.50 ± 3.8	0.04*
LVOT parameters				
SAM at rest	19 (15.1%)	10 (9.5%)	9 (42.9%)	0.001*
Rest LVOT gradient (mmHg)	7 [8]	7 [6]	24 [56]	0.001*
Rest LVOT gradient ≥ 50 mmHg	11 (8.7%)	2 (1.9%)	9 (42.9%)	<0.001*
Exercise LVOT gradient (mmHg)	12 [22]	10 [14]	67 [111]	0.001*
Exercise LVOT gradient ≥ 50 mmHg	16 (12.7%)	5 (4.8%)	11 (52.4%)	<0.001*
LA parameters				
LA diameter (mm)	52 ± 8	52 ± 7	57 ± 8	0.005*
LA exercise 2DS (%)	30.6 [69.5]	32.2 [22.7]	22.3 [9.7]	0.02*
LA rest 2DS (%)	26.0 [49.5]	26.8 [14.1]	21.3 [7.5]	0.13
Exercise LAVi (mL/m ²)	28 [15]	26 [15]	42 [18]	<0.001*
Rest LAVi (mL/m ²)	25 [14]	24 [13]	37 [15]	<0.001*

For abbreviations, see legend of Table 1.

HCM and MR

MR has been described in patients with HCM since the condition was first described in the 1960s. In 1969, Wigle et al.³¹ showed that the degree of MR varied directly with the severity of LVOTO and primarily occurred secondary to the LVOTO.

If prognosis significance of exercise-induced MR in secondary MR is noted in the latest ESC guidelines,³² as an increase in MR severity and sPAP that occurs during exercise indicates mitral surgery, there is no dedicated work published, to the best of our knowledge, regarding exercise-induced MR and HCM. Of note, quantitative

Table 3 Multivariate Cox regression for primary endpoint with stepwise selection

	HR	P
Exercise MR ≥ 2	3.24 (1.22–8.5)	0.02
Rest PAPs ≥ 35 mmHg	1.03 (0.98–1.08)	0.18
Rest LVOT gradient ≥ 50 mmHg	0.45 (0.08–2.55)	0.37

For abbreviations, see legend of Table 1.

assessment of MR is challenging in patients with HCM. The PISA-method is highly challenging with a mix between MR and the LVOT aliasing. We thus used only an observer independent and expert careful semi-quantitative assessment of the MR in our study. By the way, this study is the first to show a potential relationship between prognosis and exercise-induced MR. MR, which is a common phenomenon in HCM, has two main aetiologies. SAM and severe LVOT obstruction may result in failure of normal leaflet coaptation and, thus MR. This phenomenon is dynamic in nature and its severity varies with the degree of LVOT obstruction.³³ These findings may explain why it is important to evaluate MR at exercise and not only at rest. They also explain the strong association that we found between exercise-induced MR and exercise-induced LVOT gradient. Mitral leaflet morphological abnormalities (such as elongation) or papillary muscle abnormalities also cause MR in HCM.³⁴ Regarding mitral valve morphological abnormalities, Sriram *et al.*³⁵ showed that bileaflet mitral valve prolapse was associated with life-threatening ventricular arrhythmia.

Thus significant exercise-induced MR may define a group of patient with either a severe LVOT obstruction or morphologic abnormalities who have a higher risk of cardiovascular events.

Limitations

First, this study is limited by the size of the studied population and the fact that the study was performed by only one team. Unfortunately, we observed only a limited number of events during the follow-up. Larger studies with longer follow-up periods are thus needed. As medications were not withdrawn before test, LVOT gradient may have been blunted by the 75.4% of patients who were receiving beta-blockers (interrupting the treatment was judged un-ethical). Exercise-echocardiography protocols are not currently standardized-enough. It is thus, difficult to compare our study and published works. Precise evaluation of exercise-induced MR is challenging because PISA is usually merged with the LVOTO aliasing.

Clinical perspectives

Exercise echocardiography, with patients on their medications, should be considered in the routine implication of HCM, because several recent studies found that peak LVOT gradient ≥ 50 mmHg is an indicator of worse outcome. Also exercise-induced MR should probably be looked for especially for a best prediction of rhythmic events.

Conclusion

Exercise-induced MR and exercise LVOT gradient ≥ 50 mmHg may impact outcomes in HCM patients. Exercise-induced MR was the only echocardiographic parameter linked to SCD in our study. MR has several causes in HCM but the strong relationship between exercise-induced MR and LVOTO is confirmed as important.

Acknowledgements

We thank deeply the 'ligue contre la cardiomyopathie' for the grant we got to perform the study. Thanks also to Patricia Bouillet for her assistance in following the patients.

Conflict of interest: none declared.

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3.3. Différenciation CMH et cœur d'athlète grâce aux nouveaux outils

Nos résultats précédents ont démontré que l'analyse des paramètres de déformations myocardiques était un outil intéressant pour caractériser les CMH. Par ailleurs, nous avons démontré que l'évaluation de ces paramètres à l'effort était possible et permettait de mettre en évidence des différences non visibles au repos.

Nous avons donc souhaité utiliser cette technique afin d'améliorer la distinction entre l'HVG pathologique et l'HVG physiologique. Des études antérieures ont certes démontré que le strain longitudinal global (GLS) de repos était altéré dans les CMH par rapport aux athlètes ²⁹⁻³³. Mais, aucune de ces études n'avait comparé des athlètes avec et sans CMH. Dans la suite de l'étude réalisée en collaboration avec le groupe du Professeur Sharma ⁶¹, il nous est paru essentiel de lever ce biais en incluant des athlètes avec une CMH.

Apport du candidat dans ce travail

Conception du projet. Inclusion de la majorité des sujets. Analyse de l'ensemble des données.
Rédaction du manuscrit.

RESUME [*Article soumis au British Journal of Sports Medicine*]

Objectifs: Des études antérieures ont démontré que le strain longitudinal global (GLS) de repos était altéré dans les cardiomyopathies hypertrophiques (CMH) par rapport aux athlètes. Néanmoins, ces résultats ont été établis à partir d'études comparant des athlètes sains et des sédentaires porteurs d'une CMH. Aucune étude n'a comparé des athlètes avec et sans CMH.

Méthodes et résultats: 36 athlètes avec une CMH ont été inclus prospectivement, ils ont été appariés sur l'âge à 36 CMH sédentaires, 36 athlètes sains et 36 sédentaires sains. Les 2 groupes d'athlètes ont été appariés sur la durée d'entraînement et les 2 groupes de CMH sur l'épaisseur pariétale maximale. Les 144 patients ont bénéficié d'une échocardiographie de repos et durant un effort sous-maximal. Le GLS a été mesuré, la déviation standard des délais du pic de raccourcissement myocardique évalué par le strain longitudinal a été calculée afin de rendre compte de la dispersion mécanique. Les CMH sédentaires avaient la valeur de GLS la plus basse au repos et à l'effort. Le GLS de repos n'était pas différent entre les athlètes CMH et les 2 groupes contrôles, mais à l'effort le GLS a permis de différencier les athlètes avec ou sans CMH. La dispersion mécanique était plus élevée dans les 2 groupes CMH par rapport aux 2 groupes contrôles au repos et à l'effort. Les courbes ROC ont montré que dans le groupe d'athlètes la dispersion mécanique ($AUC=0.949\pm0.023$) avait une meilleure capacité à identifier les CMH que le GLS au repos ($AUC=0.644\pm0.069$) ($P<0.001$) ou à l'effort ($AUC=0.706\pm0.066$) ($P<0.005$).

Conclusion: Chez l'athlète, à l'inverse du GLS de repos, le GLS à l'effort peut aider à diagnostiquer une CMH. La dispersion mécanique du strain longitudinal est un marqueur précoce de la pathologie et semble donc être un outil d'avenir pour le diagnostic différentiel entre CMH et cœur d'athlète.

**Value of mechanical dispersion by strain echocardiography
for the diagnosis of hypertrophic cardiomyopathy in athletes.**

Short Title: Mechanical dispersion in HCM athletes

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Key words: Hypertrophic cardiomyopathy, athletes, strain, mechanical dispersion, exercise echocardiography

Word count: 2.957

ABSTRACT:

Background: The distinction between hypertrophic cardiomyopathy (HCM) and athlete's heart remains challenging. Previous studies have demonstrated that resting global longitudinal strain (GLS) is altered in HCM patients in comparison to athletes. Nevertheless these results rely on studies comparing healthy athletes to sedentary HCM, none provided an appropriate comparison between athletes with and without HCM.

Methods: We prospectively included 36 athletes with HCM, matched on age with 36 sedentary HCM patients, 36 healthy athletes and 36 sedentary controls. Both athlete groups were matched on training duration and HCM groups on maximal wall thickness.

All subjects underwent an echocardiography at rest and during a submaximal exercise. GLS was assessed, and standard deviation of time to maximum myocardial shortening of longitudinal strain was calculated as a parameter of mechanical dispersion.

Results: HCM sedentary group showed the lowest resting and exercise GLS. Resting GLS was not different between HCM athletes and the 2 control groups but exercise GLS enabled to differentiate HCM athletes from healthy athletes. Mechanical dispersion was higher in both HCM groups vs. both control groups at rest and during exercise. ROC analysis in the athlete groups demonstrated that resting mechanical dispersion ($AUC=0.949\pm0.023$) had better ability to identify HCM compared with GLS at rest ($AUC=0.644\pm0.069$) ($P<0.001$) or during exercise ($AUC=0.706\pm0.066$) ($P<0.005$).

Conclusion: In athletes, exercise GLS but not resting GLS can help for the diagnosis of HCM. Mechanical dispersion of longitudinal strain is an early sign of disease, which seems to be a promising tool for the diagnosis of HCM in athletes.

SUMMARY BOX:

What are the new findings?

- HCM athletes and HCM sedentary patients have a different phenotype with a better systolic and diastolic function in HCM athletes. This makes the diagnosis of HCM more challenging in athletes.
- Global longitudinal strain (GLS) at exercise but not at rest can differentiate HCM athletes from healthy athletes.
- Myocardial dispersion of longitudinal strain seems to be a promising tool to differentiate HCM athletes from healthy athletes.

How might it impact on clinical practice in the near future?

- We must use different diagnostic criteria's when assessing an athlete and a sedentary HCM patient.
- A normal global longitudinal strain (GLS) at rest cannot be used to exclude the diagnosis of HCM in an athlete. A decrease in exercise GLS seems to be an earlier sign of disease.
- We should take into account the mechanical dispersion, which seems even more promising than exercise GLS for the diagnosis of HCM

INTRODUCTION

Regular intense physical activity can induce electrical and myocardial adaptations referred to as “athlete’s heart”.[1] Morphological adaptations are characterized by an enlargement of the cardiac chambers associated with an increase in left ventricle (LV) wall thickness. In most cases the athlete’s heart diagnosis is easy. However, despite clinical and cardiac imaging characteristics proposed to differentiate athlete’s heart and hypertrophic cardiomyopathy (HCM),[2] in few cases doubt may persist. Yet, this diagnosis is important, as HCM is one of the most common causes of sudden cardiac death in young athletes.[1]

The use of strain analysis is now recommended in HCM as a clinical tool for the evaluation of LV systolic function.[3] Thus, a decrease in global longitudinal strain (GLS) has been proposed to distinguish HCM from athlete’s heart.[4-7] Furthermore, it has been shown that because of myocardial disarray and fibrosis, the systolic contraction in HCM is heterogeneous in contrast with the homogenous contraction in athletes.[8] The main weakness of these studies was that they compared HCM sedentary with healthy athletes.[4-8] Indeed, it has been reported that some athletes with proven HCM are able to exercise at very high levels, probably because of a good LV compliance.[9,10] In the same way a recent paper proposed that HCM athletes present a better systolic and diastolic functions than HCM sedentary.[11] But to our knowledge, resting GLS has not been compared in HCM athletes and in sedentary HCM.

Moreover, it must be underlined that previous results concerned only resting state; although the evaluation of athlete’s heart response to exercise seems promising.[12] GLS analysis during exercise is still scarce even if its feasibility and its interest have already been reported in previous studies in healthy athletes and in HCM patients.[7,13,14]

Thus, the aims of this study were (i) to compare the resting 2D strain patterns in HCM sedentary and in HCM athletes and (ii) to study the effect of exercise on these GLS patterns. For these purposes, four populations, HCM athletes, HCM sedentary, healthy athletes and sedentary controls were included.

METHODS

Study population

From December 2008 to May 2013, 36 athletes with HCM were prospectively and consecutively enrolled. They were matched on age with 36 HCM sedentary, 36 healthy athletes and 36 sedentary controls. Sedentary (HCM and controls) subjects practiced ≤ 1 h/week of moderate physical activity during all their life. Athletes (HCM and healthy) trained > 4 h/week during the last 5 years and regularly took part in competition at inclusion. Both athlete groups were matched on training duration and sport type. At the time on initial medical evaluation all HCM-athletes were still training.

All participants were included and follow-up in one single regional French HCM reference center. Diagnosis of HCM was performed because of symptoms or work-up of cardiovascular abnormalities (mainly ECG abnormalities) during familial screening or competitive sport's pre-participation evaluation. The diagnosis of HCM was based on LV hypertrophy (LVH) > 16 mm in any myocardial segment, as assessed on echocardiography and cardiac MRI (CMR), in the absence of another cardiac disorder or systemic condition able to produce the same level of LVH.[15] In cases of mild LVH (15 mm), HCM was diagnosed with an association of features, including (1) identification of HCM in a first-degree relative; (2) nonconcentric patterns of LVH; (3) dynamic left ventricular outflow tract obstruction; (4) late gadolinium enhancement (LGE) on CMR.[11][15] Importantly, the isolated association of

electrocardiographic anomalies and mild concentric LVH was not considered for diagnosis of HCM. All individuals had baseline blood pressure (BP) <140/90 mm Hg.

Both HCM groups were matched on maximal wall thickness.

Exclusion criteria for HCM patients were, depressed LV ejection fraction (LVEF≤50%), persistent atrial fibrillation (AF), history of coronary artery disease, and inability to perform a maximal stress test.

All subjects provided informed consent to participate in the study. The study was performed in accordance with the principles outlined in the Declaration of Helsinki on research in human subjects (CNIL declaration n°909378).

Study protocol

All subjects underwent the same day, a clinical examination, a resting 12-lead electrocardiogram (ECG), a transthoracic echocardiography at rest and during submaximal exercise and a maximal cardiopulmonary exercise test (CPET).

All HCM subjects also underwent a CMR the same day. When adapted, the HCM patients were asked to withhold beta-blockers treatment 24 hours before evaluation.

Echocardiography

All subjects underwent a resting and an exercise echocardiography with a Vivide9 (GE Healthcare, Horten, Norway). Exercise echocardiography was performed on an integrated electromagnetic cycle ergometer tilt table (Ergometrics, Lynnwood, WA, USA). The initial workload was 30 Watts; with 30-Watts increment every 2 min. As previously described, echocardiographic data were recorded at a sub-maximal stage with a stable heart rate between 100-120 beats/min in order to be able to perform accurate strain measurements.[13,14]. ECG was recorded continuously, and BP was measured every 2 min.

The standard acquisitions, parasternal, apical, and subcostal views, were recorded during resting and exercise echocardiograms. All data were stored on a workstation for offline analysis (Echo PAC BT12, GE Healthcare, Horten, Norway) by a cardiologist blinded to the clinical data. The conventional analysis of the echocardiogram preceded the 2D strain analysis. For each measurement, at least two cardiac cycles were averaged. LV end diastolic diameter (LVEDd, mm) and the maximal end diastolic LV wall thickness (MWT, mm) were measured in parasternal views.[15] The LV and end-systolic volumes (LVED vol., LVES vol., ml) and EF (%) were measured by the biplane method of discs. Peak E-wave and A-wave velocities of the mitral inflow were measured using pulsed wave Doppler. Tissue Doppler imaging was recorded at the level of septal and lateral mitral annulus, to obtain the average peak velocities during systole (s') and early (e') diastole. E/e' was calculated in order to assess the LV filling pressure.

Mitral regurgitation (MR), if present, was graded in four grades (0–4 from mild to severe) following the PISA method; LV outflow velocities were measured at rest and during exercise. Strain measurement was based on the speckle tracking approach: circumferential, radial and global longitudinal myocardial deformations were evaluated from standard 2D images (frame rates 60-90 sec^{-1}). Radial (GRS) and circumferential (GCS) strains were the average of the segment strains at mid parasternal short axis view. Global longitudinal strain (GLS) was the average of the 18 segment strains from the apical 4-3 and 2 chamber views.[16] Post-systolic shortening was not included in the global strain analysis. The time to maximum myocardial shortening, including post systolic shortening if present, was measured from the ECG onset Q/onset R-wave in the 18 LV segments (figure 1). As proposed, we used the SD of the 18 time intervals to maximum myocardial shortening to quantify LV mechanical dispersion.[17] 2D strain measurements were also performed on the left atrium (LA),[18] the peak atrial

strain was obtained during ventricular systole (measured at the end of the reservoir phase), after averaging the 12 segmental curves obtained on a apical 4 and 2 chambers view.[18]

Cardiopulmonary exercise test (CPET)

All subjects performed a progressive maximal exercise test on ergocycle (ERG 900, Jaeger, Hochberg, Germany) according to Wasserman recommendations.[19] Exercise was symptom limited or stopped at exhaustion. A passive recovery 6 minute's period was also recorded. Breath by breath gas exchanges were analysed with an Oxycon device (Eric Jaeger, Hoechberg, Germany) and ECG (CardioSys, Marquette-Hellige, Freiburg, Germany) was continuously monitored, seeking of arrhythmias and/or repolarization alterations. The BP was measured every 2 minutes using a manual manometer. Maximal oxygen uptake (VO_2) peak was expressed as a percentage of predicted value.

Cardiac magnetic resonance imaging

All HCM patients underwent a CMR using a Siemens Avanto 3-T CMR (Siemens Healthcare, Germany). A standard cardiac volume, wall dimension, function, and LGE sequence was performed with full myocardial coverage based on the CMR society guidelines.[20] LV volume, mass, and function were quantified using customized analysis software by a blinded, single experienced investigator. Diastolic wall-to-volume ratio was measured.[21] Imaging for LGE to identify fibrosis was performed 5-10 minutes after 0.1mmol/kg gadolinium contrast injection and was analyzed qualitatively.[20]

Follow-up

HCM patients were followed up clinically every 6 months. The mean duration of follow-up was determined using the most recent evaluation as of April 1st of 2014, or when adapted the

patient's death. Cardiac events included cardiac death, appropriated intra cardiac defibrillator (ICD) discharge, acute heart failure event requiring hospitalization, new onset of AF or ventricular tachycardia including non-sustained ventricular tachycardia (NSVT).

Statistical Analysis

Gaussian distribution of all continuous variables was confirmed with a Kolmogorov-Smirnov test, and values are reported as mean \pm SD. Comparisons between the 4 groups were performed with ANOVA tests, followed when appropriate by a Bonferroni test. Comparisons between the two HCM groups were performed using a Student's t test and a chi-square test.

Receivers operating characteristic (ROC) curves were created and areas under curves (AUC) were calculated for the ability of GLS and mechanical dispersion at rest and exercise to identify HCM. A 2-tailed value of $p < 0.05$ was considered as significant.

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois). ROC curves analysis and pairwise comparison were performed using MedCalc version 15.2.2 (MedCalc Software, Ostend, Belgium).

RESULTS

Demographic parameters and CPET characteristics of the 4 groups

As requested by inclusion criteria, the physical training duration was similar in both trained groups (6.3 ± 2.9 h/week in HCM athletes and 7.3 ± 4.3 h/week in healthy athletes; $P = 0.880$) (table 1). The exercise capacity of HCM athletes (108.1 ± 21.1 % of predicted VO_2 peak value) was markedly lower than the healthy athletes one ($166.7 \pm 24.1\%$), higher than the HCM sedentary one (74.9 ± 16.5 %) and similar to the exercise capacity of sedentary controls ($110.7 \pm 21.6\%$).

HCM patient characteristics

No difference was observed concerning CMR characteristics between the 2 HCM groups (table 2). Indeed, both groups had similar LV mass, MWT, LVED vol., diastolic wall-to-volume ratio and presence of LGE (58% vs. 39% in HCM sedentary and HCM athletes respectively; $P=0.176$). .

Nevertheless, due to a higher rate of dyspnea in sedentary-HCM patients, symptoms were more frequent at inclusion in sedentary than in HCM athletes. Indeed only 8.3% of HCM were asymptomatic vs. 58.3% of HCM athletes ($P < 0.0001$) (table 2).

During follow-up (2.4 ± 1.4 years), there was also a higher occurrence of cardiac events in sedentary than in HCM athletes (25.0% vs. 8.3% respectively, $p=0.032$). AF was the only cardiac event observed in HCM athletes ($n=3$); whereas HCM sedentary suffered from cardiac death ($n=1$) ventricular arrhythmias ($n=5$; associated with appropriate discharge of their ICD in 2 patients), hospitalization for heart failure ($n=1$) and atrial fibrillation ($n=2$).

Echocardiographic characteristics

Echocardiographic characteristics are presented in table 3.

Cardiac geometry:

As defined in the inclusion criteria, the MWT was markedly thicker in both HCM groups than in controls. None of the healthy athletes had a $MWT > 13\text{mm}$. No difference was observed in MWT between HCM sedentary and HCM athletes ($20.1 \pm 3.4\text{mm}$ vs. $18.8 \pm 5.6\text{mm}$ respectively; $p=0.561$). Healthy athletes showed the largest LV (LVEDd and LVED vol.) and HCM patients had the smallest volumes, with no difference between the 2 HCM groups.

LV systolic function:

HCM sedentary had the lowest longitudinal LV function (lowest s' and GLS values) at rest and during exercise. HCM athletes presented similar resting GLS values than the control groups. During exercise, GLS was lower in HCM athletes than in healthy athletes.

The resting radial strain was not different in the four groups; during exercise radial strain was reduced in both HCM groups as compared to controls.

Mechanical dispersion of the longitudinal strain was altered at rest and during exercise in HCM athletes and in HCM sedentary as compared to controls, demonstrating a non-uniform systolic contraction of the different myocardial segments in the HCM patients.

LV diastolic function:

Resting and exercise E/A ratio were not different in the 4 groups. But both HCM-groups showed lower relaxation (e') and higher LV filling pressures (E/e') than control groups at rest and during exercise. HCM sedentary showed the lowest e' and LA strain at rest and during exercise.

LV obstruction and mitral insufficiency:

LV outflow tract obstruction (LVOTO) was only observed in HCM patients (4 vs. 2 at rest; and 7 vs. 10 during exercise in HCM sedentary and HCM athletes respectively). The mean MR was higher in HCM sedentary than in the three other groups at rest and during exercise. Three HCM sedentary showed a MR grade ≥ 2 at rest and 7 during exercise and only 1 sedentary control showed a MR ≥ 2 during exercise with no further abnormality.

ROC curves to identify HCM

ROC analysis (table 4 and figure 2) showed that resting mechanical dispersion at rest had a better ability to identify HCM as compared to GLS in the global population, and in the athletes and sedentary subgroups ($P < 0.05$ in all).

Mechanical dispersion at rest was also more accurate to depict HCM than GLS at exercise in the global population and in the athlete subgroup ($P < 0.05$ in both), but not in the sedentary group ($P = 0.484$). The use of mechanical dispersion during exercise did not improve the diagnostic accuracy as compared to mechanical dispersion at rest.

DISCUSSION

In this study, we clearly demonstrated that HCM athletes and HCM sedentary present a different phenotype. Indeed, HCM athletes have a better systolic and diastolic function than HCM sedentary associated with a better functional status and a lower incidence of cardiac events during follow-up than HCM sedentary. These phenotypic differences make the diagnosis of HCM in athletes even more challenging. Our results show that a normal GLS cannot be used to exclude the diagnosis of HCM in an athlete; whereas decrease in exercise GLS seems to be an earlier sign of disease. Nevertheless, myocardial dispersion of longitudinal strain seems to be a promising tool to differentiate HCM athletes from healthy athletes.

Comparison between HCM sedentary and HCM athletes

The clinical data and VO_2 peak values (table 1 and 2) showed that HCM sedentary presented a more severe disease than HCM athletes. Our data are in accordance with a previous publication by Sheikh et al. who demonstrated that systolic function evaluated by EF and Doppler imaging (s') was less altered in HCM athletes than in HCM sedentary.[11] The new finding of our study is that we observed the same results with resting and submaximal exercise GLS evaluation. As previously reported, diastolic function was also more decreased

in HCM sedentary than in HCM athletes.[11] Indeed, e' and LA reservoir function were lower in HCM sedentary than in HCM athletes. All these differences in diastolic function were obvious at rest, and submaximal exercise echocardiography did not provide any complementary information.

From our data, we cannot exclude that the less altered systolic and diastolic functions observed in HCM athletes might be due to the beneficial effects of training.[22] However, these differences might more likely be the sign of a less severe myocardial disease in HCM athletes which could therefore explain that they were still able to train intensively at the moment of their inclusion in the study.[9,10] Indeed, it was previously shown that in HCM patients decrease in GLS was associated with dyspnea [23] and was an independent predictor of cardiac events.[24-26]

Mechanical dispersion was previously described in post myocardial infarction patients as a marker of myocardial scar.[8,17] In HCM, mechanical dispersion might be related to myocardial fibrosis and disarray.[8,27] Thus the similar mechanical dispersion in both HCM groups might be explained by a similar rate of LGE and the same degree of hypertrophy in both groups. In previous series, mechanical dispersion was predictive of arrhythmic events [8,17], nevertheless no ventricular events occurred during the follow-up period in the HCM athletes group. We can speculate that the sample size of the population was too small to assess the prognostic value of mechanical dispersion in this specific population.

Comparison of HCM athletes and healthy athletes

Using the conventional criteria the distinction between both groups of athletes was easy to perform. Indeed MWT was markedly thicker, LV cavity was smaller and diastolic function was altered in HCM athletes as compared to healthy athletes.[15,28] Despite these huge differences in structural characteristics and diastolic function, resting longitudinal, radial and

circumferential strains were not different between the two groups of athletes. Only the mechanical dispersion of GLS was increased in HCM athletes. During exercise, an alteration in longitudinal and radial strains occurred; mechanical dispersion was still increased in HCM athletes in comparison with the two controls groups.

We can therefore hypothesize that increase in mechanical dispersion and alteration of GLS during exercise are early signs of myocardial disarray and fibrosis in HCM patients making these parameters suitable for early diagnosis in athletes. Indeed, we observed a decrease of resting GLS only in the more severe HCM sedentary patients.

Clinical implications:

Our results have significant practical implications for the diagnosis of HCM in athletes. Indeed, a normal value of GLS at rest will not exclude the diagnosis of HCM in an athlete. GLS at exercise might be helpful to perform the diagnosis of HCM, but mechanical dispersion seems an easier and more accurate tool.

Limitations and perspectives

We only performed submaximal exercise, because the accuracy of strain analysis during maximal analysis seems currently difficult. Nevertheless, we might speculate that a maximal exercise might emphasize even better the differences between HCM patients and controls.

It could have been valuable to include athlete-controls with a borderline wall thickness (14-15mm). Indeed, the healthy athletes had a slightly increased wall thickness in comparison to sedentary controls, but only 3 athletes had a MWT of 13mm. We chose to exclude borderline athletes, in whom HCM diagnosis might have been missed by current methods. Thus, further studies including athletes in the “grey zone” for HCM diagnosis are needed.[28]

CONCLUSION

A normal GLS at rest is not sensitive enough to discard the diagnosis in athletes suspicious of HCM. The use of exercise echocardiography increases the diagnosis value of GLS. However, mechanical dispersion of longitudinal strain is an early sign of disease, which seems to be a promising tool for the diagnosis HCM in athletes.

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Table 1: Subjects characteristics

	HCM sedentary (n=36)	HCM athletes (n=36)	Sedentary controls (n=36)	Healthy athletes (n=36)	P value
Demographics					
Male/female	33/3	34/2	36/0	36/0	0.133
Age (years)	40.6±10.2	38.1±16.5	37.1±16.1	41.0±16.7	0.636
BSA (m ²)	1.9±0.2	1.9±0.2	1.9±0.1	1.9±0.1	0.467
Physical training (h/week)	0 ^{*‡}	6.3±2.9 [#]	0	7.3±4.3	<0.0001
VO ₂ peak (% of predicted value)	74.9±16.5 ^{*‡‡}	108.1±21.1 ^μ	110.7±21.6 [¶]	166.7±24.1	<0.0001

BSA: body surface area

**HCM sedentary vs. HCM athletes; † HCM sedentary vs. Sedentary controls; ‡ HCM sedentary vs. Healthy athletes; # HCM athlete vs. Sedentary controls; μ HCM athletes vs. healthy athletes; ¶ Sedentary controls vs. Healthy athletes*

Table 2: HCM patients characteristics

	HCM sedentary (n=36)	HCM athletes (n=36)	P value
Clinical parameters			
Asymptomatic at inclusion (%)	8.3	58.3	<0.0001
Chest pain (%)	19.4	5.6	0.075
Palpitation (%)	30.6	22.2	0.422
Syncope (%)	16.7	13.9	0.743
Dyspnea (%)	61.1	8.3	<0.0001
Abnormal ECG (Q wave, PTWI or ST depression) (%)	88.9	88.9	1.0
Familial history of HCM (%)	41.7	33.3	0.465
Familial history of SCD (%)	16.7	13.9	0.743
Cardiac event during FU (%)	25.0	8.33	0.032
FU duration (years)	2.5±1.4	2.3±1.4	0.494
CMR parameters			
MWT (mm)	19.7±4.3	17.8±6.7	0.215
LV mass (g)	190.6±87.9	186.0±65.7	0.843
LVED vol. (ml)	149.5±41.6	157.4±28.2	0.755
MWT/ LVED vol. indexed (mm.ml ⁻¹ .m ²)	0.26±0.07	0.22±0.08	0.125
Presence of LGE (% of patients)	58	39	0.176

TWI: pathological T-wave inversion; SCD: sudden cardiac death; FU: follow-up; CMR: cardiac magnetic resonance; MWT: maximal wall thickness; LV: left ventricle; LVED vol.: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; LGE: late gadolinium enhancement.

Table 3: Echocardiographic data at rest and at submaximal exercise

Parameter		HCM sedentary (n=36)	HCM athletes (n=36)	Sedentary Controls (n=36)	Healthy athletes (n=36)	P value
HR (bpm)	Rest	64.5±13.1	68.6±14.2 ^μ	68.0±8.2 [¶]	59.5±12.0	0.003
	Ex.	109.3±13.2 [‡]	112.5±6.5	115.8±5.2	111.2±4.6	0.008
Power (W)	Ex.	89.9±34.2 [‡]	98.6±44.1 ^μ	98.8±21.6 [¶]	125.0±32.5	<0.0001
sBP (mmHg)	Rest	132.5±18.9	133.3±20.5	124.0±9.6	127.0±12.1	0.063
	Ex.	159.7±37.3	171.3±33.7	168.4±29.5	181.9±24.8	0.064
CI (L/min/m ²)	Rest	2.8±1.1	3.0±0.9	2.5±0.6	2.7±0.9	0.202
	Ex.	6.1±2.9	5.7±1.9	5.0±1.2	6.2±2.4	0.090
MWT (mm)	Rest	20.1±3.4 ^{‡‡}	18.8±5.6 ^{μμ}	9.1±1.2	11.0±1.4	<0.0001
LVEDd (mm)	Rest	43.5±6.7 [‡]	42.9±5.4 ^{μμ}	46.8±3.8 [¶]	51.9±5.1	<0.0001
LVED vol. (ml)	Rest	92.5±30.5 ^{‡‡}	98.2±20.8 ^μ	112.5±22.3 [¶]	139.1±29.6	<0.0001
	Ex.	84.6±30.9 ^{‡‡}	84.4±28.1 ^{μμ}	114.3±19.5 [¶]	142.8±32.0	<0.0001
LVEF (%)	Rest	63.2±8.4 [*]	69.9±6.6 ^{μμ}	64.1±6.3	62.8±6.3	<0.0001
	Ex.	67.1±10.3 ^{*‡}	73.5±9.3	72.1±5.6	70.5±5.2	0.006
s' (cm/s)	Rest	8.3±2.2 ^{*‡‡}	9.9±2.1	10.6±2.4	9.9±1.7	<0.0001
	Ex.	9.8±2.0 ^{*‡‡}	13.4±2.5	14.2±3.1	13.0±3.3	<0.0001
GLS (%)	Rest	-15.0±3.3 ^{*‡‡}	-17.4±3.5	-18.1±1.7	-19.0±1.8	<0.0001
	Ex.	-17.8±4.0 ^{*‡‡}	-21.2±3.6 ^μ	-22.4±3.0	-23.6±2.1	<0.0001
Mechanical dispersion (msec)	Rest	62.5±20.5 ^{‡‡}	60.0±18.6 ^{μμ}	30.8±13.7	30.7±9.1	<0.0001
	Ex.	51.3±21.4 ^{‡‡}	44.6±15.4 ^{μμ}	22.3±10.3	22.8±5.8	<0.0001
Circumferential strain (%)	Rest	-16.2±4.8	-18.3±4.0	-17.6±4.1	-16.7±3.4	0.214
	Ex.	-16.5±9.8	-20.9±5.4	-20.1±4.8	-21.2±3.0	0.051
Radial strain (%)	Rest	35.6±14.7	39.8±13.0	42.5±10.5	38.0±12.1	0.174
	Ex.	38.2±17.5 ^{‡‡}	39.4±15.1 ^{μμ}	50.6±16.3	50.8±9.4	0.003
E/A	Rest	1.35±0.70	1.53±1.00	1.44±0.50	1.58±0.59	0.539
	Ex.	1.41±0.73	1.20±0.33	1.12±0.19	1.39±0.58	0.084
E/e'	Rest	10.4±4.1 ^{‡‡}	8.6±3.8 ^{μμ}	4.9±2.1	3.6±2.1	<0.0001
	Ex.	11.1±3.1 ^{‡‡}	9.8±5.1 ^{μμ}	5.4±2.1	4.3±2.3	<0.0001
e' (cm/s)	Rest	8.4±2.2 ^{*‡‡}	11.0±3.3 ^{μμ}	13.8±3.5	14.1±4.1	<0.0001
	Ex.	11.2±3.2 ^{*‡‡}	15.2±4.4 ^{μμ}	19.3±3.5	20.0±4.3	<0.0001
iLA vol (ml/m2)	Rest	24.0±8.8	24.0±10.6	19.2±6.7 [¶]	27.7±7.8	0.001
	Ex.	29.6±12.8 [‡]	24.0±9.0 ^μ	20.0±5.8 [¶]	31.0±7.8	<0.0001
LA strain (reservoir) (%)	Rest	25.6±9.3 ^{*‡‡}	33.9±10.6	38.0±8.8	39.3±8.2	<0.0001
	Ex.	31.9±13.6 ^{*‡‡}	47.3±15.8	54.5±18.8	47.9±10.0	<0.0001
MR (mean)	Rest	0.4±0.7 ^{*‡‡}	0.1±0.2	0.0±0.2	0.1±0.4	<0.0001
	Ex.	0.7±1.0 ^{*‡‡}	0.1±0.3	0.1±0.3	0.1±0.3	<0.0001
LVOTO≥30mmHg (%)	Rest	11.1	5.5	0	0	0.054
	Ex.	19.4 ^{‡‡}	27.8 ^{μμ}	0	0	<0.0001

HR: heart rate; sBP: systolic blood pressure; CI: cardiac index; MWT: maximal wall thickness; LVED d and vol.: left ventricular end diastolic diameter and volume; LVEF: left ventricular ejection fraction; iLA vol.: indexed left atrial volume; LA strain: left atrial strain; MR: mitral regurgitation; LVOTO: left ventricular outflow tract obstruction.

*HCM sedentary vs. HCM athletes; † HCM sedentary vs. Sedentary controls; ‡ HCM sedentary vs. Healthy athletes; # HCM athlete vs. Sedentary controls; μ HCM athletes vs. healthy athletes; ¶ Sedentary controls vs. Healthy athletes

Table 4: ROC Curves, accuracy of GLS and mechanical dispersion to identify HCM patients

		AUC	P value	Cut-off value	Se	Sp
Global population	Rest GLS	0.711±0.045	<0.0001	-17.0	56.9	88.9
	Ex. GLS	0.761±0.042	<0.0001	-21.2	70.0	80.6
	Rest mechanical dispersion	0.935±0.021	<0.0001	40.4	91.6	84.2
	Ex. mechanical dispersion	0.940±0.022	<0.0001	33.6	82.9	96.4
Athletes	Rest GLS	0.644±0.069	0.036	-16.8	44.4	97.2
	Ex. GLS	0.706±0.066	0.002	-21.3	55.9	94.4
	Rest mechanical dispersion	0.949±0.023	<0.0001	40.4	94.3	88.9
	Ex. Mechanical dispersion	0.915±0.036	<0.0001	31.0	82.4	91.7
Sedentary	Rest GLS	0.781±0.057	<0.0001	-17.0	69.4	86.1
	Ex. GLS	0.827±0.050	<0.0001	-18.0	61.1	94.4
	Rest mechanical dispersion	0.920±0.036	<0.0001	43.1	86.1	85.7
	Ex. mechanical dispersion	0.950±0.037	<0.0001	33.6	91.7	95.0

GLS: global longitudinal strain; Ex.: exercise; AUC: area under the curve

FIGURES LEGEND

Figure 1: example of 2D strain curves in a healthy athlete and in an HCM athlete

GLS: global longitudinal strain; MD: mechanical dispersion assessed by the standard deviation of the 18 segments (for the clarity of the figure only 6 segments are shown)

Figure 2: ROC curves, accuracy of GLS and mechanical dispersion to identify HCM patients

GLS: global longitudinal strain

** $P < 0.05$ as compared to GLS at rest; † $p < 0.05$ as compared to GLS during exercise*

Figure 1:

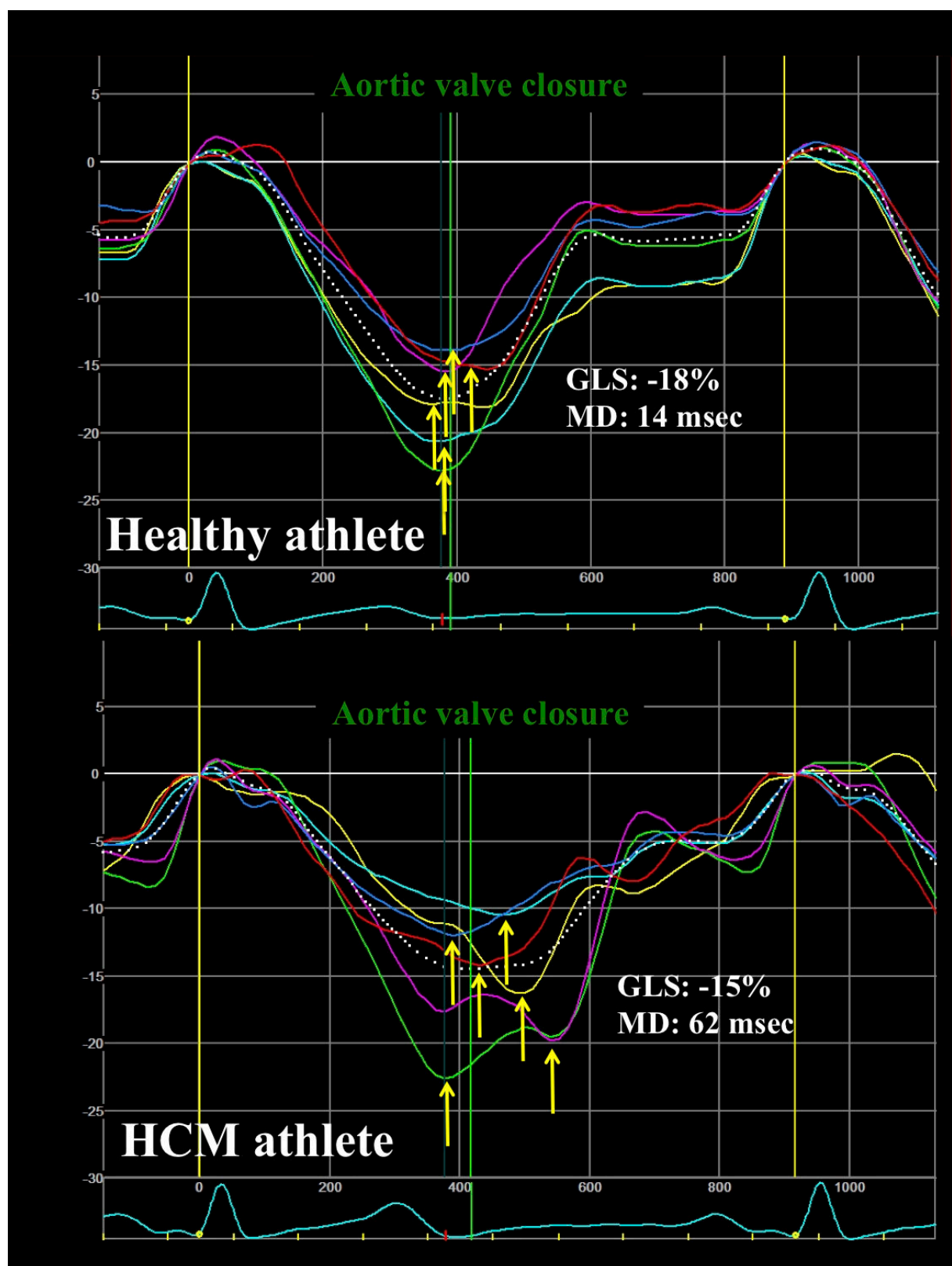
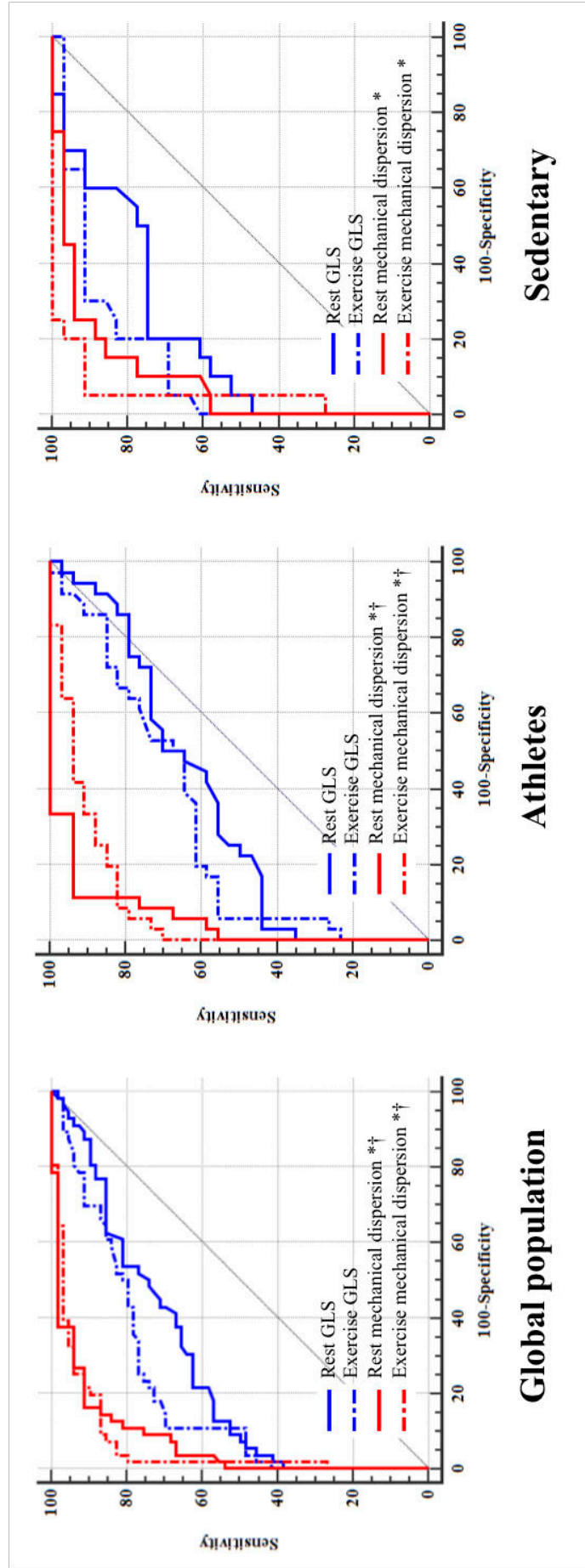


Figure 2:

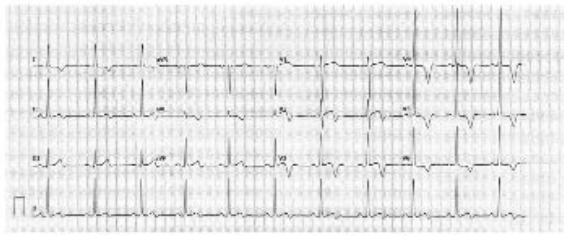


Partie 5: DISCUSSION et PERSPECTIVES

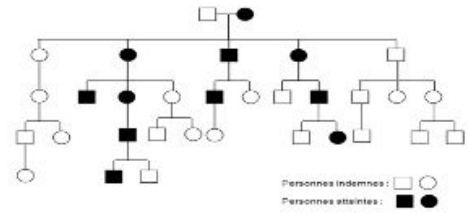
L'ensemble de ces travaux a permis

1. d'améliorer le dépistage de la CMH chez l'athlète en améliorant les critères diagnostiques ECG de l'athlète.
2. de définir une stratégie multiparamétrique pour mieux poser le diagnostic de cardiopathie chez l'athlète avec ondes T négatives, notamment en intégrant dans l'évaluation initiale, outre la réalisation d'une échocardiographie et d'une exploration à l'effort, la réalisation d'une IRM myocardique.
3. De démontrer que les athlètes avec CMH ont un profil phénotypique moins sévère avec une HVG moins importante, des cavités ventriculaires plus larges et de meilleurs indices de fonction diastolique. Par ailleurs, les données de 2D strain longitudinal sont le plus souvent normales. Néanmoins, l'exploration de ces athlètes à l'effort a permis de mettre en évidence une altération du 2D strain longitudinal à l'effort. La dispersion mécanique du strain longitudinal semble être un marqueur précoce de la pathologie et semble donc être un outil d'avenir pour le diagnostic différentiel entre CMH et cœur d'athlète.
4. Cette altération de la dispersion mécanique dans les CMH semble être en lien avec la fibrose macroscopique, même si d'autres facteurs interviennent dans l'altération du 2D strain tels que le type d'hypertrophie et la post-charge.

CMH ou coeur d'athlète ?



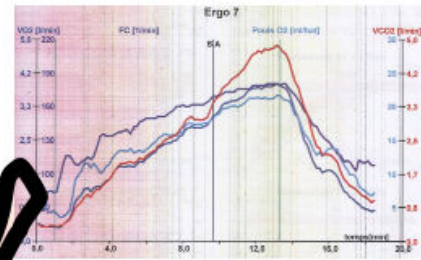
ondes T négatives pathologiques



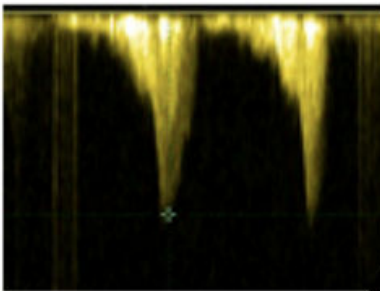
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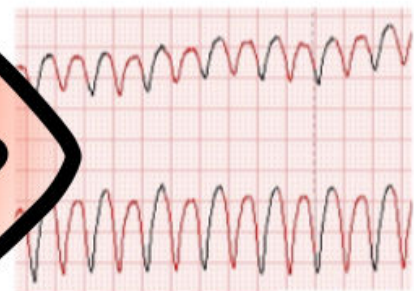
Hypertrophie pariétale
sans dilatation VG



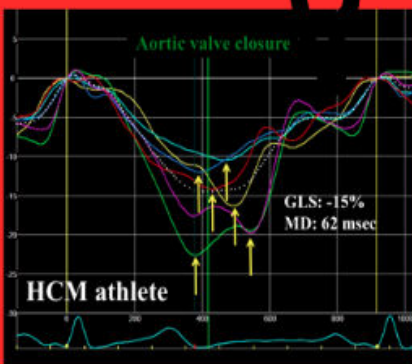
Altération du pic de VO2



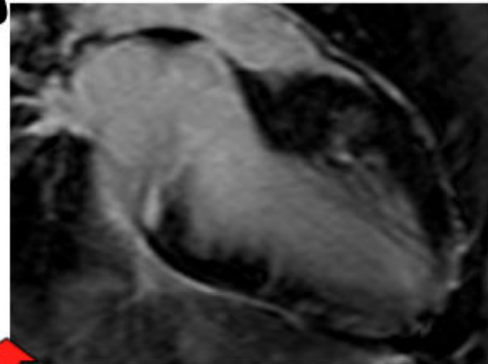
SAM
gradient intra VG



Arythmies ventriculaires



Strain à l'effort
et dispersion mécanique



Rehaussement tardif

Figure 10 : Approche multiparamétrique pour différencier CMH et cœur d'athlète

1. Amélioration du dépistage ECG chez l'athlète

Avec le développement des connaissances de l'interprétation de l'ECG, chaque nouvelle classification ECG permet de diminuer le taux de faux positifs, permettant ainsi d'espérer une amélioration de la rentabilité et de l'acceptabilité du dépistage de la population des sportifs. Dans la classification proposée dans ce travail ⁶², nous avons considéré que l'hypertrophie atriale gauche et droite, la déviation axiale gauche et droite, l'hypertrophie ventriculaire droite et les ondes T négatives biphasiques jusque V4 chez l'athlète afro-caribéen n'étaient pathologiques que si au moins deux de ces modifications étaient présentes. Ceci a permis de diminuer le nombre de faux positifs, particulièrement chez l'athlète afro-caribéen.

L'autre élément important dans notre travail, a été de démontrer que les ondes T négatives pathologiques chez l'athlète étaient associées à une pathologie cardiaque dans 44.5% des cas. Nous avons par ailleurs démontré qu'il convenait de réaliser un bilan exhaustif initial comportant échocardiographie, test d'effort, Holter ECG et également une IRM myocardique. Même en cas de normalité de ce bilan, 5 sujets ont développés une cardiomyopathie au cours du suivi. Il convient donc de suivre attentivement ces sujets.

Perspectives : Outre les problèmes de classification ECG par des experts, la principale limitation à la généralisation du dépistage ECG est qu'elle doit pouvoir être réalisée par l'ensemble des médecins du sport, voire l'ensemble des médecins généralistes. Une des perspectives futures de notre travail serait d'améliorer les logiciels de lecture automatique de l'ECG en intégrant les données définies par nos critères affinés. Dans les algorithmes d'analyse automatique de l'ECG il serait important de pouvoir intégrer le niveau d'entraînement sportif ainsi que l'âge et l'ethnie. Ceci permettrait un meilleur dépistage des anomalies ECG par l'ensemble des médecins réalisant une visite de non contre-indication à la pratique sportive en compétition.

2. CMH chez l'athlète, un phénotype morphologique particulier

Les athlètes avec CMH ont un profil phénotypique moins sévère avec une HVG moins importante, des cavités ventriculaires plus larges et de meilleurs indices de fonction diastolique. Par ailleurs, les données de 2D strain longitudinal sont le plus souvent normales chez ces sujets. Ceci peut expliquer pourquoi certaines CMH sont capables de réaliser des performances inhabituelles sans symptômes ^{42,43}. Néanmoins, l'exploration de ces athlètes à l'effort a permis de mettre en évidence une altération du 2D strain longitudinal à l'effort. La dispersion mécanique du strain longitudinal semble être également un marqueur précoce de la pathologie et semble donc être un outil d'avenir pour le diagnostic différentiel entre CMH et cœur d'athlète.

Perspectives : Dans les études de validation précédentes, nous avons déterminé que l'altération du 2D strain (tant en valeur qu'en délais de pic de contraction) est au moins en partie liée à la fibrose myocardique, même si d'autres facteurs interviennent dans l'altération du 2D strain (la post charge, le degré d'hypertrophie).

Il n'est pas question de remplacer l'IRM par les seules données de déformations myocardiques, mais il pourrait être envisagé de mieux sélectionner grâce à ces données les sujets chez lesquels il faut réaliser une IRM myocardique ceci afin d'éviter de multiplier les examens complémentaires. En effet, même si dans le cadre des ondes T négatives pathologiques 24 sujets avaient une IRM anormale alors que l'échocardiographie était normale, il ne faut pas oublier que 94 sujets (60%) avaient une IRM normale.

Bien entendu, avant de pouvoir intégrer ces données en pratique clinique, il est indispensable de les valider sur des cohortes multicentriques.

3. Apport d'autres techniques ?

- **Apport du T1 mapping :**

Certaines techniques n'ont pas été abordées dans ce manuscrit. C'est le cas des données de quantification de la fibrose interstitielle en IRM par les techniques de T1 mapping ⁶³. Il est probable que ces techniques vont connaître un essor dans les années à venir.

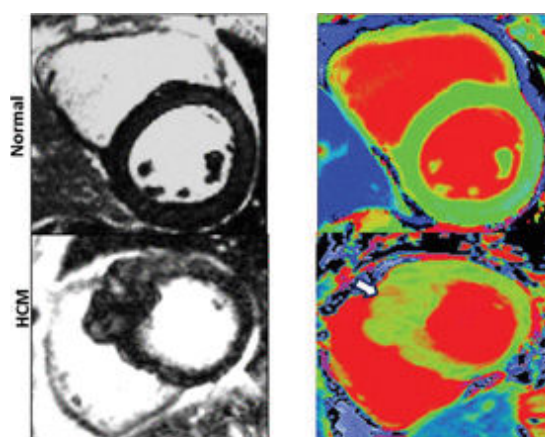


Figure 11 : Exemple de cartographie de T1 mapping chez un sujet normal et une CMH, D'après Dass S, JACC 2012.

- **Apport de la génétique :**

L'apport de la génétique n'a également pas été développé dans ce travail. Il est évident qu'en cas de mutation pathologique retrouvée chez un athlète avec suspicion de cardiopathie le diagnostic est certain. Cependant, les résultats des analyses génétiques ne sont pas toujours évidents à interpréter compte tenu de nombreux variants de signification non déterminée.

4. Stratification du risque

Le challenge le plus important à relever n'est peut être plus de dépister correctement les CMH, mais plutôt de stratifier correctement le risque individuel en cas de pathologie.

En effet, nous avons démontré que le phénotype des athlètes avec CMH est différent de celui des sujets sédentaires. Ceci n'est probablement pas le fait du remodelage physiologique induit par le sport, mais probablement le fait d'une pathologie moins sévère les rendant capable de réaliser du sport en compétition.

Pour le moment, la découverte d'une CMH contre-indique la pratique sportive en compétition ainsi que toute activité de sport intense⁵. Néanmoins, du fait d'un dépistage de plus en plus efficace, il est probable que nous allons dépister des cardiopathies de plus en plus « discrètes » qui n'auraient pas été diagnostiquées avec des outils moins sensibles et qui n'auraient peut-être jamais eu de traduction clinique.

Pour le moment aucune étude visant à faire pratiquer du sport intense aux CMH n'a encore été réalisée. Mais cela a déjà été réalisé dans d'autres situations à risque chez l'athlète, comme le syndrome du QT long⁶⁴ ou chez les sujets implantés de défibrillateurs automatiques implantables⁶⁵.

Cette stratification plus précise du risque passe évidemment par des études prospectives incluant un suivi longitudinal d'athlètes présentant une CMH.

CONCLUSIONS

Les travaux que nous avons menés et auxquels nous avons collaboré ont permis de développer des outils pour mieux différencier une HVG pathologique d'une HVG physiologique mais également pour mieux caractériser cette HVG et déterminer avec plus de précision le pronostic des CMH.

Nous avons proposé une nouvelle classification ECG permettant de mieux repérer les athlètes avec modifications ECG non pathologiques sans diminuer pour autant la spécificité de détection des CMH. En cas d'ondes T négatives chez l'athlète, nous avons démontré qu'il était indispensable de réaliser une IRM myocardique. En effet l'échocardiographie peut être prise en défaut dans près de 35% des cas.

Néanmoins, les critères diagnostiques actuels de CMH peuvent être pris en défaut. En effet les athlètes avec une CMH ont un phénotype différent des sédentaires avec CMH avec une meilleure fonction systolique et diastolique et également une meilleure fonction longitudinale. L'évaluation de la fonction longitudinale à l'effort et l'évaluation de la dispersion mécanique sont des paramètres qui semblent prometteurs en termes de diagnostic. L'altération de la fonction longitudinale semble être en lien avec la fibrose myocardique, même si d'autres facteurs comme la masse VG, le type de CMH et les conditions de charge influent sur la fonction longitudinale.

L'échocardiographie d'effort, notamment la présence d'une insuffisance mitrale à l'effort, permet de mieux évaluer le pronostic des patients atteints de CMH.

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LISTE des PUBLICATIONS et des COMMUNICATIONS

ARTICLES PUBLIES DANS LE CADRE DE LA THESE (7)

1. **Schnell F**, Riding N, O'Hanlon R, Axel Lentz P, Donal E, Kervio G, Matelot D, Leurent G, Doutreleau S, Chevalier L, Guerard S, Wilson MG, Carré F. Recognition and significance of pathological T-wave inversions in athletes. *Circulation*. 2015 Jan 13;131(2):165-73.
2. **Schnell F**, Donal D, Bernard Brunet A, Reynaud A, Wilson M, Thebault C, Ridard C, Mabo Ph, Carré F. Strain analysis during exercise in patients with left ventricular hypertrophy: impact of etiology. *J Am Soc Echocardiogr*. 2013 Oct;26(10):1163-9
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5. Sheikh N, Papadakis M, **Schnell F**, Panoulas V, Malhotra A, Wilson M, Carré F, Sharma S. The clinical profile of athletes with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging*; 2015 Jul;8(7):e003454
6. Reant P, Donal E, **Schnell F**, Reynaud A, Daudin M, Pillois X, Dijos M, Landelle M, Peyrou J, Cornolle C, Laurent F, Montaudon M, Roudaut R, Lafitte S. Clinical and imaging description of the Maron subtypes of hypertrophic cardiomyopathy. *Int J Cardiovasc Imaging*. 2015 Jan;31(1):47-55.
7. Sheikh N, Papadakis M, Ghani S, Zaidi A, Gati S, Adami PE, Carre F, **Schnell F**, Wilson M, Avila P, McKenna WJ, Sharma S. Limitations of current ECG interpretation recommendations in young athletes: a call for a paradigm shift with focus on African and Afro-caribbean ethnicity. *Circulation*. 2014 Apr 22;129(16):1637-49

ARTICLE EN COURS DE SOUMISSION DANS LE CADRE DE LA THESE (1)

1. **Schnell F**, Matelot D, Daudin M; Kervio G, Mabo P, Carré F, Donal E. Value of mechanical dispersion by strain echocardiography for the diagnosis of hypertrophic cardiomyopathy in athletes. British Journal of Sports Medicine

COMMUNICATIONS ORALES ET AFFICHEES DANS LE CADRE DE LA THESE

Communications orales congrès internationaux : (1)

1. Euro Prevent Congress 2015:
Interpreting the ECG : An asymptomatic athlete with T-wave inversion; let sleeping dog lie ?

Communications orales congrès nationaux: (18)

1. Printemps de la Cardiologie 2009: Séance SFC / jeunes cardiologues en formation.
Longitudinal myocardial function and exercise. Interest for differentiating physiologic from pathologic left ventricular hypertrophies
2. Journées Européennes de la Société Française de Cardiologie (JESFC) 2010:
Communications libres.
Valeur ajoutée de la fonction myocardique longitudinale au repos et à l'effort pour différencier les hypertrophies ventriculaires gauches physiologiques et pathologiques
3. JESFC 2012: Communications libres.
Relative importance of the afterload and the myocardial disarray on left ventricular longitudinal function. A rest and standardized exercise study.
4. Printemps de la Cardiologie 2012: Table Ronde GERS/FFC/SFC
Electrophysiologie du coeur du sportif- Cardiomyopathie ou coeur d'athlète
5. Comité National Olympique et Sportif Français (CNOSF) 2012.
Conférence nationale médicale interfédérale du CNOSF. Bilan cardiovasculaire des athlètes de haut niveau français
6. Congrès Coeur et Sport 2012: Atelier débat Médical /Biopharma
Comment éliminer une insuffisance cardiaque chez le sportif ?
7. JESFC 2013: Session pratique des cardiologues en formation
Sport et échocardiographie
8. Printemps de la cardiologie 2013: Séance à thème. Actualité 2013 en imagerie
Recherche translationnelle en écho/IRM
9. Congrès coeur et sport 2013: Quoi de neuf en cardiologie du sport en 2013?
Anomalie de la repolarisation chez l'athlète
10. Paris Echo 2013: Atelier pratique. Speckle tracking: principales applications.

Cardiomyopathies, coeur de sportif

11. Paris Echo 2013: Session à thème. Rôle de l'échocardiographie en cardiologie du Sport- Rôle du speckle tracking et de l'échocardiographie 3D pour évaluer un coeur d'athlète.
1. Réunion Scientifique de la filiale d'échocardiographie aux JESFC 2014:
Alteration of longitudinal deformation is due to fibrosis in hypertrophic cardiomyopathy
2. JESFC 2014: Session commune GERS/ Rythmologie/SFC
Certificats de non contre indication au sport - Sport et valvulopathie aortique
3. Congrès Coeur et sport 2014: Actualités en 2014. ECG de repos, quelle classification utiliser ? 26^e congrès du CNCF 2014: Sport et anomalies de la repolarisation. Bilan devant des troubles de la repolarisation de l'athlète
4. Réunion Scientifique de la filiale d'échocardiographie aux JESFC 2015:
Understanding alteration of longitudinal deformation in hypertrophic cardiomyopathy: insights from multimodality imaging
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(Nom et Prénom)